FIRST AMERICAN SURGICAL ASSOCIATION NUMBER

Vol. LXXXII JULY, 1925 No. 1

ANNALS of SURGERY

A Monthly Review of Surgical Science and Practice

Edited by

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J. B. LIPPINCOTT COMPANY, PUBLISHERS

MONTREAL PHILADELPHIA LONDON

ANNALS of SURGERY

VOL. LXXXII JULY, 1925 No. 1

MECHANISM OF THE FORMATION AND GROWTH OF MALIGNANT TUMORS*

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WE CAN hardly expect to cure malignant tumors, or to prevent their occurrence, as long as the factors determining their formation and the conditions of their growth remain unknown. The problem of cancer must be attacked from its physiological side. We have to discover by what process a group of cells acquires the power to proliferate indefinitely among the dormant tissues of the adult animal. The growth of cancer is certainly determined by conditions as precise as those ruling the development of normal tissues. It is true that malignant cells do not obey the common law. But their anarchical appearance must be attributed merely to our lack of knowledge of the properties causing their peculiar behavior. If we knew all the factors capable of producing cell proliferation and dedifferentiation, we could understand the genesis of cancer. Conversely, the discovery of the nature of malignant tumors would certainly advance our knowledge of the mechanisms of tissue growth. Instead of merely searching for the virus, bacteria, helminths, or chemical substances that may be responsible for the occurrence of cancer, or studying the fate of transplanted bits of tumors in animals, we must consider the problem in its physiological aspects and elucidate the fundamental relations which unite the development of neoplasms, the proliferative energy of normal tissues, and the functions of the humors.

The mechanisms that bring about the resting condition of the tissues in the adult organism, and allow a resumption of their activity during wound healing or tumor growth, are most complex. However, the experimental analysis of these phenomena has become possible lately. The new technics, by which fibroblasts, epithelial cells, leucocytes, and tumor cells can be made to grow in pure cultures like bacteria,[1] have brought some light into this obscure field. This paper is intended merely to bring together certain facts that I have observed in studying normal and cancer tissues, and to discuss their significance from both points of view—the formation of tumors, and their growth.

A. Mechanism of the Formation of Malignant Cells.—The transformation of normal into malignant cells takes place under conditions that are far from being accurately known. However, it is certain that tumors practically always occur at the site of a chronic irritation, sarcoma appearing

* Read before the American Surgical Association, May 5, 1925.

during youth, and carcinoma during old age. These simple observations indicate that two factors are necessary for the production of cancer—local irritation, and a certain condition of the tissues and the humors, such as takes place in old age or youth. No specific agent can be held responsible for the formation of a tumor. An immense amount of clinical evidence and the observations of Borrel, Fibiger, Yamagiwa, and others have proven that cancer develops as readily in the focus of a parasitic or bacterial infection as in tissues irritated by X-ray burns or some chemical substances. But, in order to bring about the formation of a tumor, these irritants generally require a certain predisposition of the organism, such as senescence in the case of carcinoma.

Our problem is to discover how local irritation determines a neoplasm and how this phenomenon may be influenced by a general condition of the organism. The study of transplanted tumors cannot give us any information, as we are concerned with the transformation of normal into cancer cells, and not with their mode of propagation. Fortunately, it has become possible to observe the genesis of a tumor since Rous found a sarcoma which can be transmitted through its filtered extract. This discovery can be considered the most important advance in cancer research during the last twenty-five years, because it rendered feasible a direct examination of the process of tumor formation. More recently, Yamagiwa also developed an effective method of producing cancer tissue by coal tar. The formation of a neoplasm by this technic is a slow process, while the filtered extract of Rous' sarcoma possesses such activity that the transformation *in vitro* of normal tissue into sarcoma may take place in two days.[2] However, both Rous' substance and coal tar were used in my investigations of the genesis of malignant cells, the rôle of irritation in the process, and the mechanism of body resistance to tumor formation.

Transformation of Normal into Malignant Cells by Rous' Principle.—When an extract of Rous' sarcoma, filtered through a Berkefeld filter, is injected into a chicken, a malignant tumor develops which generally kills the animal by lung metastases. The tumor, as is well known, is a spindle-cell sarcoma, which is to-day extremely malignant and may bring about the death of the host in about two weeks. When a fragment of Rous' sarcoma is cultivated *in vitro,* cells of various types migrate into the culture medium. They are chiefly polymorphonuclear leucocytes, macrophages, and fibroblasts. We had to determine whether all these cells are malignant, or whether the malignant characteristic belongs only to one type. From Rous' sarcoma and another chicken sarcoma, pure strains of fibroblasts and of large mononuclear leucocytes (monocytes, blood macrophages, or endothelial leucocytes) were isolated, and after a few weeks their malignancy was tested by inoculation into chickens. The fibroblasts were not found to be malignant,[3] while the pure cultures of macrophages, when grafted into fowls, gave rise to tumors which killed the animals rapidly.[4] Although Rous' sarcoma consists of spindle cells, it appeared that the malignant element is the macrophage.

The result of these experiments indicated that the inoculation of Rous' substances into the body probably transforms the tissue macrophages into sarcoma cells, while it has little or no action on the fibroblasts. This supposition was tested *in vitro*. Pure cultures of fibroblasts and of blood macrophages were inoculated with the cancer-producing substances. The fibroblasts did not become transformed into malignant cells,[5] while the macrophages did.[6] It was obvious that the macrophages possess a stronger affinity for Rous' substance than the fibroblasts. The Rous sarcoma appears, therefore, to be a disease of the macrophage. In some of Fischer's experiments,[7] where fragments of embryonic heart became sarcomatous from contact with fragments of Rous' tumor, the contamination was probably due to infection of the tissue macrophages by Rous' principle. When heart tissue is inoculated *in vitro* with sarcoma extract, the abnormal migration of the tissue macrophages, which was observed by Ebeling,[8] shows that these cells have been affected by Rous' substance in some manner. But it is not unlikely that under certain conditions fibroblasts can also be infected.

The possibility of transforming a pure strain of normal monocytes into sarcoma has been utilized in the study of the essential characteristics of a malignant cell.[9] Pure cultures of monocytes taken from the blood were made in flat, round flasks and subsequently inoculated with a small amount of filtered Rous' sarcoma extract. After several weeks, the cultures were injected into fowls and gave rise to rapidly growing tumors which ultimately killed the animals by metastasis. It was evident that the monocytes had become sarcomatous. The changes undergone by such cultures may be summarized as follows:

After the inoculation of cultures of monocytes with Rous' substance, most of the cells go on multiplying for days or weeks. But a few macrophages assume the appearance of diseased cells and sometimes agglutinate in clumps. Around the small masses of amorphous tissue, the ameboid cells show less activity, become full of vacuoles and granulations, metamorphose into fibroblasts,[9, 10, 11] and eventually die. It seems as if Rous' substance communicates to the monocytes a disease which still allows the cells to multiply, but shortens their life.

When the culture medium is stained with phenol red, it becomes apparent that the tissues infected with Rous' principle manufacture more acid than the controls, even before the onset of marked morphological changes.[2] The acid production may be more marked when the medium contains a large amount of glucose and is deprived of air. This agrees with the fact discovered by Warburg, that tumor tissue, deprived of oxygen, possesses a high glycolytic power. The production of acid by the cells, as well as their diseased condition, explains the increase of their electrical conductivity observed by Crile. This modification of the conductivity is a characteristic of cell injury, as Osterhout has shown, and also of an increase of the H ion concentration in the tissues. It can hardly be considered as specific of tumors.

The cultures are profoundly modified by the production of necrotic tissue

and the digestion of the medium around the amorphous masses. The coagulum assumes the appearance of a geographic map or moth-eaten cloth. There is an abundant production of proteolytic enzymes which later on destroy the medium and eventually kill the cultures. Numerous monocytes become transformed into large triangular, polygonal, or spindle-shaped cells, having sharp processes and filled with granulations. They closely resemble normal or diseased fibroblasts.

During the process, the Rous principle is reproduced, as is demonstrated by the formation of malignant tumors after fowls have been inoculated with the fluid of the cultures.[9]

We may conclude from these experiments that the essential characteristic of a sarcomatous macrophage is to be a diseased and short-lived cell which reproduces the substance responsible for its malignant transformation. The tumor cell is by no means anarchical, nor does it possess as much growth energy as a normal monocyte. It is merely a sick cell. The malignant transformation is not the result of a long process, as cultures of normal spleen have been observed to become sarcomatous in forty-eight hours.[2]

The morphological changes in a pure culture of monocytes under the influence of Rous' principle remind one of the clear areas that Twort observed developing in his cultures of micrococcus after he had inoculated it with the lytic principle, called later bacteriophage by d'Herelle. In those areas, the micrococci underwent lysis and reproduced the lytic principle, and the phenomenon could repeat itself indefinitely. In an analogous manner, the macrophages inoculated with Rous' substance become sick, reproduce the Rous substance, and die. As long as the coagulum contains living cells, the Rous substance is set free in the medium. There is some resemblance between the lytic principle of Twort and the Rous principle. Both can be supposed to develop within a cell under the influence of a metabolic disturbance, caused by a non-specific factor. Once the process has started, it reproduces itself indefinitely by a mechanism that we do not understand, but whose existence is certain.

The properties that we have described as characteristic of the malignant cells of Rous' sarcoma are probably common to all sarcomatous cells. An investigation was made of the behavior *in vitro* of various types of malignant tumors [2] such as carcinoma of the hen ovary, other fowl sarcomas, Flexner-Jobling carcinoma, mouse carcinoma, mouse sarcoma, fowl coal tar sarcoma, fowl teratoma, and human spindle-cell sarcoma. In every case, the cells were less active than normal cells of the same type and died prematurely. The digestion of the medium took place generally in the same manner as in cultures of Rous' sarcoma. A more complete study was undertaken of tar sarcoma.[2] Its cultural properties closely resemble those of Rous' sarcoma. The fragments rapidly surround themselves with polymorphonuclear leucocytes and macrophages. These cells are less resistant than normal leucocytes and monocytes and die in large numbers within twenty-four hours. The digestion of the medium occurs in the usual way. In the digested area, small

clumps of amorphous material, dying macrophages, and large fibroblasts more or less full of granulations and vacuoles are observed. After a few days, the cultures present the same appearance as the cultures of Rous' sarcoma. To summarize: there is no fundamental difference between the cultural characteristics of the Rous and tar sarcomas, and most of the properties of the macrophages from both tumors are identical.

We do not yet understand the mechanism of the transformation of normal cells into tumor cells under the influence of coal tar. In spite of the large number of experiments inspired by the discovery of Yamagiwa, little is known beyond the fact that coal tar rubbed on the skin, or injected into the tissues, brings about the formation of a malignant tumor.

In order to analyze this phenomenon more closely, Landsteiner and I attempted to transform a pure strain of fibroblasts into sarcomatous cells by adding small amounts of coal tar to the cultures. The experiments were continued for months. Some morphological changes were observed, but none of the cultures became malignant. Later, I performed similar experiments with macrophages, also with negative results. It appeared that coal tar did not directly induce the transformation *in vitro* of the normal cells into tumor cells and that its mode of action differs in a radical way from that of Rous' substance.[2]

Therefore, I supposed that coal tar could be considered as the probable precursor of a substance analogous to Rous' principle which develops in the tissues of the animal under the influence of two factors, local irritation, and a modification of the blood plasma produced by coal tar. This hypothesis inspired the following experiments.[2] Some chickens, into which Miss McFaul had injected intravenously a solution of coal tar, were inoculated under the skin with a small amount of embryonic pulp. This gave rise to teratomas which were partly sarcomatous, recurred after extirpation, and produced tumor when grafted into other fowls.

This result signifies that the simultaneous action of both factors, embryonic pulp, and a condition of the humors, brought about by intravenous injection of tar, may result in the formation of a tumor. Tar cancer would be a self-perpetuating disturbance of the metabolism created by the action on embryonic cells of a substance contained in the humors and related directly or indirectly to coal tar. The knowledge of this effect may lead to some understanding of the causation of other tumors. It is plausible to think that certain substances produced by bacteria and helminths, or resulting from X-ray burns, may determine in macrophages or epithelial cells, as does coal tar, a disturbance which afterwards propagates itself indefinitely. By a similar mechanism, the toxic substances normally present in the blood during old age might act on the dividing cells of an irritated area as does the serum of tar-injected chickens on embryonic pulp. This simple process would be responsible for the spontaneous production within the organism of malignant tumors.

Effect of Local Irritation on the Formation of Sarcoma.—Cancer almost

always starts at the site of a chronic inflammation, as every surgeon knows. But this effect of local irritation on the formation of a neoplasm is not yet well understood. Rous has observed that the formation of tumors under the influence of sarcoma extract is facilitated by local irritation. Starting from his experiments, I made a study of the mechanism of the phenomenon.[2] At first, I found that such slight inflammation as was supplied by the presence of a small fragment of woolen cloth in the subcutaneous tissue caused the Rous substance to produce a tumor at a concentration as low as 1 per 50,000, and later that irritative factors of widely different nature increase the effect of Rous' principle on the tissues. As those factors have in common the property of inducing a slight inflammation, possibly their effect is due to the leucocytes attracted to the irritated area, or to the substances secreted by them. These two suppositions were submitted to experimental test.

After the inoculation of some cultures of leucocytes, spleen, and embryonic heart with equal amounts of Rous' filtered extract, the sarcomatous transformation occurred more quickly in the cultures of leucocytes and spleen than in the heart cultures.[2] In other experiments, a small amount of pulp of embryonic tissue was injected into chickens at the same time as Rous' principle. Tumors developed much earlier and were about five times larger than those produced by the sarcoma substance alone.[2]

We also ascertained whether, at body temperature, the presence of embryonic substances increases the duration of the activity of the Rous agent *in vitro*.[2] It is well known, since Rous studied this subject, that the cancer-producing substance is very unstable and loses its activity in a short time at body temperature, when it is dissolved in saline solution and in serum. But in serum, the life of the principle is a little longer than in saline. Recently, I repeated those experiments and confirmed the early results of Rous. Under the present conditions, Rous' substance dissolved in Tyrode solution generally disappears after an incubation of fifteen hours, while it is still active if dissolved in serum. When fresh tissue and embryonic juice are added to the serum, the agent can be preserved several hours longer and, under certain conditions, as long as four days.

The mechanism of local irritation on the formation of sarcoma by Rous' principle can now be understood more clearly. We have to explain by what process a very small amount of Rous' principle fails to produce any effect when injected alone into the tissues, but determines the appearance of a tumor if the tissues are slightly irritated. The failure of the injection into non-irritated tissues can be attributed to the absence of macrophages, and to the lack of susceptibility of adult fibroblasts to Rous' substance. If the sarcoma agent is only in contact with resistant cells, it spontaneously loses its activity within a short time, and no tumor occurs. But if the tissues receiving the injection are inflamed and contain leucocytes and their juices, they become more susceptible to the Rous agent. As the sarcoma-producing substance remains active for a longer time under these conditions, it has still more chance of meeting with susceptible cells which then become malignant.

Mechanism of the Natural Resistance of the Organism to the Formation of Sarcoma.—When mice are rubbed with coal tar, or fowls are inoculated with diluted Rous agent, some of them develop tumor and others do not. It is obvious that the formation of tumors under the action of a given factor requires a certain predisposition, or lack of resistance of the organism, which can be compared to the susceptibility shown by the tissues of old human beings to the development of carcinoma. Several years ago, Rous discovered that some normal chickens are immune to the inoculation of the filtered extract of sarcoma, while others are not. It is evident that the same cause does not produce the same effect in every animal. Certain individuals are more susceptible than others to the production of tumor. As this is a very important phenomenon, I have attempted to elucidate its mechanism.[2]

First a method was developed by which the resistance of an animal to the Rous principle could be roughly measured. The virulence of Rous' sarcoma has increased so markedly that a small amount of extract injected into an adult chicken always determines the appearance of a tumor. All individuals appear to be susceptible to pure extract. Differences in their resistance are detected only when diluted extract is used. The highest dilution that produces a tumor can be considered as the measure of the susceptibility of the animal. A series of chickens were grafted under the skin with small disks of flannel, soaked in solutions of Rous' sarcoma extract, varying in concentration from 1 per 1000 to 1 per 50,000, and the highest dilution producing a tumor was taken as an index of susceptibility. In some of the animals, all the dilutions, even the highest, determined a sarcoma. In others, no tumors at all were observed, or they only appeared at certain dilutions. According to the concentration of the Rous agent which initiated a neoplasm, the animals were distributed into several classes and their susceptibility or resistance was determined in some measure.[2]

The degree of resistance of an individual to Rous' sarcoma seems to be a permanent characteristic. A few chickens that were immune at a first inoculation were injected again three or four times in the course of a year, and remained immune. Other chickens were sensitive and developed tumors which were removed quickly in order to prevent the occurrence of metastases. Some of these animals survived, and were inoculated again after a few months. They were as susceptible as after the first inoculation. One of the chief causes of susceptibility to the influence of the Rous substance was age. Young animals are always less resistant than old ones, or than animals affected with any wasting disease.[2]

Since a few apparently normal chickens resist the effect of the Rous substance, there is certainly some mechanism which protects the immune or relatively immune animal against the action of the infecting agent. We may suppose that in the less susceptible animals the Rous principle loses its activity under the influence of the humors before it has a chance of infecting the tissues, or that the macrophages have less affinity for it than those of susceptible animals, or that they are not present in sufficient numbers. The

first hypothesis was verified by testing *in vitro* the effect of the serum of immune and susceptible animals on the Rous agent.[2] By treating the serum of a number of animals which were susceptible or immune to sarcoma with a small amount of Rous' principle, incubating it for some hours, and inoculating a fowl with disks of flannel soaked in the fluid, we determined whether the sarcoma principle had lost its activity under the influence of the serum. Generally, the agent loses its tumor-producing power more rapidly in the serum of immune than in that of susceptible animals. Under the conditions of my experiments, the Rous substance which had been incubated with Tyrode solution, guinea hen serum, duck, or rabbit serum, ordinarily did not produce any tumors. When incubated with serum of susceptible fowls, it gave rise to sarcoma. Generally the mixture of Rous' principle and serum of immune animals failed to develop a neoplasm, or determined the appearance of a tumor after a longer time. It appears, then, that the serum of the susceptible animals differs chiefly from that of non-susceptible animals in being a better preservative medium for the Rous principle. In order to arrive at some understanding of this phenomenon, I studied the effect of certain modifications of normal serum on the preservation of Rous' principle.[2] When serum had been heated at 70° C., its property of retarding the spontaneous destruction of Rous' substance was practically lost. The serum of young fowls was generally found to be a better preservative medium than that of old ones. There is probably some relation between the affinity of Rous' principle for macrophages and embryonic cells and its prolonged activity in young serum.

Individual susceptibility is partly determined by a certain condition of the humors which depends on the age of the animal, its metabolism, state of health, possibly its diet, and many other factors, especially heredity. There are certainly other causes of this phenomenon, but we have as yet no precise knowledge of them. The existence of a general condition of the organism, which modifies its resistance to sarcoma, is of great practical importance. It is not impossible that a thorough knowledge of the mechanism which brings about resistance may ultimately lead to the development of methods for decreasing the frequency of malignant tumors.

B. Mechanism of the Growth of Tumors.—The factors determining the transformation of normal into malignant cells are not identical with those that induce the tumor to grow indefinitely within the organism. In order to understand the development of a sarcoma in an adult animal, we must find out what factors prevent the growth of normal tissues.

Regulation of the Growth of Normal Tissues.—It has been generally supposed that tissue growth comes to a standstill when the energy derived from the ovum is exhausted. This theory was disproved by a study of the regulation of cell multiplication *in vitro* which disclosed the two following facts: fragments of connective tissue taken from an adult animal can be made to proliferate as actively as embryonic tissues;[12, 2] a strain of fibroblasts in the fourteenth year of its life *in vitro* displays the same proliferating activity as embryonic tissue.[13] Therefore, it is clear that the growth energy

of adult connective tissue is not exhausted, and that the growth energy of embryonic tissue is unlimited under certain conditions. Another classical theory explains the arrest of growth of adult tissue by the pressure of other tissues. This supposition was also subjected to experimental test. When fragments of connective or epithelial tissues are extirpated from an adult animal and cultivated in serum, the cells proliferate for a while, but their mass does not increase.[14] Freedom from the pressure of surrounding tissues does not give the cells the power of synthetizing new protoplasm from serum.

The dormant condition of adult tissues must be attributed to another cause. As soon as the use of pure cultures of fibroblasts permitted the analysis of the conditions determining growth, I found that the quantity of fibroblasts produced *in vitro* in a given time depends upon the composition of the medium. In serum from an adult animal, the multiplication of fibroblasts decreases and finally stops. When embryonic tissue juice is added to the medium, the rate of growth progressively increases until the tissue fragments double in volume every forty-eight hours. In other words, the growth energy of a pure culture of cells is a function of the concentration of the growth-promoting and inhibiting substances contained in the medium.[12, 14, 15]

The growth-promoting substances are contained chiefly in embryonic juices and possess the fundamental property of rejuvenating adult connective tissue and epithelium, and of inducing an unlimited proliferation of both tissues.[16] They are easily destroyed by heating, do not pass through a Chamberland filter, and lose their activity in a short time at body temperature. They are analogous to those present in leucocytes, malignant tumors, and certain adult tissues. They differ from the hormones because they do not merely stimulate growth, but also contain the food material necessary for the synthesis of protoplasm.[17] Embryonic tissue juices have the power to maintain fibroblasts and epithelial cells in a true condition of cultivation and determine an indefinite increase in their volume.[14]

Blood serum, in which cells may proliferate for some time, does not supply fibroblasts and epithelial cells with the food material necessary for the building up of new tissues.[14, 18] It is not a nutrient medium for these cells. Serum also possesses the property of restraining cell proliferation.[19] Its growth-inhibiting power, which is slight in youth, increases progressively during the course of life and becomes very strong in old age.[20] This important property of serum is due to the antagonistic action of two groups of substances, a globulin which is slightly growth-promoting, and a compound of albumin and other substances, which is stable, resists heating, and is strongly inhibiting for cell multiplication.[21]

We had to ascertain whether blood plasma and interstitial lymph are endowed with the same restraining power as serum. When a culture of fibroblasts that has multiplied actively for years *in vitro* is grafted into a fowl, its growth stops after a few days.[1] The injection of chick embryo pulp into an adult chicken generally produces a teratoma which ceases growing after a few weeks, and acquires a growth energy as low as that of the tissues of the

host.[2] It appears that *in vivo* as well as *in vitro* the humors of the adult organism are inhibiting to cell proliferation. Another proof of the similar inhibiting properties of serum and of plasma is given by the parallel variations in the rate of wound healing according to age, and in the growth-inhibiting action of serum.[22] We may consider as certain that the inhibiting power of plasma is not markedly different from that of serum.

The organism appears to be protected against any abnormal growth of tissue by a triple mechanism, the lack in blood serum of the food material required by fibroblasts and certain epithelial cells for the synthesis of protoplasm, the growth-inhibiting power of serum, and the instability of the growth-promoting substances that may be set free in the humors. While the inhibiting substances of serum are very stable, do not disintegrate spontaneously at body temperature, and regenerate rapidly, those that promote cell multiplication are stored within the cells and, if they are set free in the humors, lose their activity at body temperature after a short time. It is clear that the organism is well protected against cell proliferation. The knowledge of this mechanism renders still more paradoxical the growth of malignant tumors which takes place in the adult animal in spite of the restraining power of the humors, and the scarcity of the growth-promoting substances.

We have to explain how cells may proliferate within the inhibiting humors. Even in senescence, dormant cells resume their former activity when necessary. Wounds heal and tumors grow as readily in old individuals as in young ones, the only difference being that the rate of cicatrization or of tumor growth is slower when the patient is old. This phenomenon may be attributed to the presence in adult and old organisms of growth-promoting substances which are stored in epithelial cells and leucocytes and can be set free in the humors.[23, 24] When, in the process of regeneration, the tissues must resume their growth activity, the inhibiting effect of blood serum is counterbalanced by substances supplied by epithelial cells and leucocytes. Leucocytes can be considered as mobile unicellular glands which bring to fixed cells the food material they require for their multiplication.[17, 24] Epithelial cells also contain nutritive substances. In the process of cicatrization, the nutrient material necessary for the formation of new cells may come from the leucocytes [24] and the epithelial cells themselves.

Regulation of the Growth of Sarcoma.—It is probable that a spindle-cell sarcoma grows within the adult organism for the same reasons that a wound cicatrizes, or an organ undergoes chronic inflammation and sclerosis. The hypothesis that tumor cells are anarchical is untenable. There is direct experimental evidence that sarcoma cells cultivated *in vitro* possess the same cultural properties as normal cells, but they are sick and die prematurely. The unlimited growth of sarcoma *in vivo* appears paradoxical when we consider that its growth energy *in vitro* is very weak. However, this phenomenon can easily be explained by the properties which were found to be characteristic of malignant cells. These cells are macrophages which can multiply easily in adult serum. They contain substances that are analagous to embryonic

trephones [17, 25] and promote cell multiplication. Besides, they invade and destroy anatomical structures such as muscles, which can be used as food material by the growing tissues. The disease that transforms the normal cells into malignant ones is characterized by its self-perpetuating power and a slow cell destruction. One of its effects is to bring about at one point the accumulation of diseased cells, which are stores of growth-promoting substances. It is obvious that if substances capable of inducing cell proliferation are constantly set free in a limited area of the organism, a tumor will develop. Such a phenomenon may explain the multiplication of fibroblasts and other cells in Rous and tar sarcoma, and also the abnormal growth energy of cartilage, bone, and epithelium that we observed in experimental teratomas when they became partly transformed into sarcoma.[2] It is clear that the growth of a tumor within the dormant tissues of an old animal does not express an anarchical tendency of a group of cells, but is caused partly by factors analogous to those of normal tissue regeneration.

It is well known that the rate of growth of a tumor of a given type depends on certain conditions of the patients and particularly on their age. Carcinoma develops rapidly in youth and slowly in old age. However, carcinoma belonging to the same histological type will grow at very different rates on people of identical age. It is obvious that the rate of growth of tumors is determined by many other factors than age. On the contrary, the variations in the rate of tissue regeneration in an aseptic wound depend entirely on the age of the patient. The relation between age and rate of wound healing in normal individuals is so constant that the age can be calculated according to du Noüy's equation, when the size of the wound and the rate of healing are known.[26] This phenomenon is due to the fact that in aseptic and non-irritated wounds, no factor other than the composition of the interstitial lymph can markedly modify the growth energy of the regenerating tissues. But when a wound is infected, the rate of healing is no longer regulated exclusively by the age of the patient, but by the substances set free by bacteria, pus, and necrotic tissue. It becomes very irregular [27] and the curve of cicatrization ceases to be expressed by du Noüy's formula. Under these new conditions, the growth energy of the regenerating cells depends on many complex influences, instead of being regulated by the normal lymph. It is probable that the growth energy of tumor cells is affected in the same manner by the substances set free by more or less diseased tissues and by the variations in the inhibiting action of blood plasma. I found that the interstitial fluid from chicken sarcoma acts on the proliferation of normal tissue in different and often opposite manners. According to the nature and the condition of the tissues, it may promote the growth of fibroblasts or, on the contrary, be toxic for them.[2] The presence of substances from normal and diseased cells and their products of disintegration modify the rate of growth of the tumor itself, as they do that of normal tissues.

The rate of growth of sarcoma is regulated, like that of wound healing, by certain conditions of the plasma which are independent of age. In cachexia

and some forms of general infection, the blood serum contains certain substances which increase its growth inhibiting action. When an abscess develops in the body of a patient having an aseptic wound, the process of cicatrization becomes very slow, and may entirely stop.[28] The same phenomenon is observed in cases of cachexia. When these conditions are reproduced in animals, the serum becomes more growth-inhibiting for fibroblasts.[29] Similar phenomena are observed in the growth of sarcoma. Their rate of growth decreases greatly when the animal becomes sick or is starved, and stops entirely in extreme cachexia.[2] In other words, there is a clear relation between the conditions which regulate the growth of sarcoma, and the rate of growth of normal tissues.

This description of the mechanism of tumor formation and growth is not intended to be an accurate expression of these complex phenomena, in any sense. Neither should my present conception of this process be taken as definitive. The bringing together of facts that are apparently disconnected is merely a convenient procedure for arriving at an understanding of their significance. New phenomena are not of scientific interest unless they are linked with what we already know and open the way to future discoveries. The interpretation of the facts which I have found in the course of my investigations will doubtless be modified. Working hypotheses only last for a short time. Their purpose is not to give an accurate interpretation of what really underlies the complexity of the phenomena, but to inspire experiments which will lead us closer to reality.

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THE TRANSPLANTATION OF DISTANT SKIN FLAPS FOR THE CURE OF INTRACTABLE BASAL-CELL CARCINOMA*

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In 1921 I reported two cases of extensive basal-cell cancer operated upon by following the principle of transplantation of distant flaps for the cure of the cancer. (Surgical Treatment of Extensive Basal-cell Carcinoma, *J.A.M.A.*, vol. lxxviii, pp. 412–416, February 11, 1922.) Since then I have had eight other patients on whom this principle was used. Though some of the operations have been too recent to justify positive deductions as to cure, it may be of interest to analyze this larger group, to consider the principle on which the therapy is based, and briefly to discuss the pathology of basal-cell cancer.

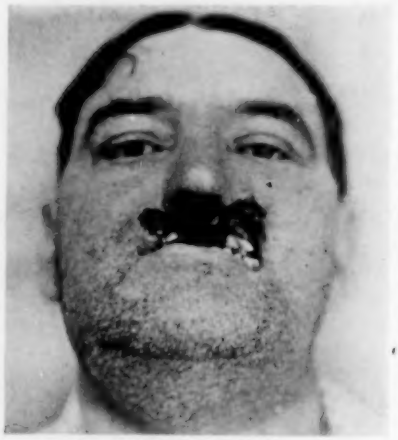

Fig. 1.—(Case I, Mr. G. K. P.). Basal cell cancer involving the upper lip, underlying bone and adjacent structures, before operation.

Two general classifications of cancers of the skin have long been recognized—the spinous-cell type and the basal-cell type. There are occasional malignant growths springing from the immediate accessory glands and appendages of the skin—the sebaceous and sweat glands and the hair follicles. The so-called melanotic sarcoma is probably in most cases epidermal in origin. A few pathologists regard basal-cell cancer as arising from the hair follicles, but it is usually considered as beginning in the deep layers of the epidermis; whereas spinous-cell cancer is supposed to originate in the superficial layers. While both of these types admit of much variation in morphology, the extremes of difference appear to be greater in basal-cell than in spinous-cell cancer.

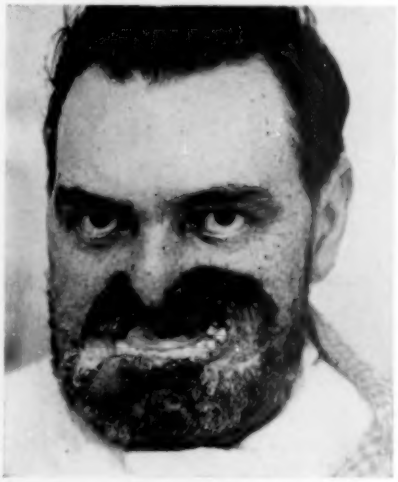

Fig. 2.—(Case I, Mr. G. K. P.). Sixteen days after operation in which the cancer was cauterized, excised, and the wound was again cauterized. The slough has not yet separated. A flap was outlined on the neck, but this does not show in the photograph.

Basal-cell cancer advances with considerable regularity at an almost uniform depth from the surface of the cancer, or

* Read before the American Surgical Association, May 5, 1925.

"rodent ulcer," as it was formerly called. Tissues opposing its march are indiscriminately attacked. The deeper layers of skin, underlying fat and connective tissue, muscle, periosteum, bone and cartilage are successively invaded in the progress of this disease. It seems to be no respecter of tissue.

The cell commonly found in basal-cell cancer is of an oblong or spindle type, sometimes drawn out into a filament. These cells are packed together and may be found in short advancing columns or in isolated groups separated by stroma from the nearby main constitute the surface of the body of similar cells which growth. (Figs. 4, 9, 10 and 13.) It is not infrequent, however, to find widely varying differences in morphology. There may be a tendency toward the development of acini with cubical or columnar cells. (Figs. 18, 22 and 23.) In some basal-cell cancers there is cystic formation, probably resulting from degeneration of central masses of cells. (Fig. 15.) Groups of cells surrounded by columnar cells like those in adamantinoma, or tubular arrangements roughly resembling the tubular glands of the stomach, are forms occasionally seen.

FIG. 3.—(Case I, Mr. G. K. P.). A month later. The slough has fully separated. The flap from the neck has been gradually dissected up until all of its nutrition comes from the pedicle and its raw surface has been partly covered by Thiersch grafts. The flap was approximated to the raw surface left by excising the cancer, after cutting away the Thiersch grafts that interfered with the approximation to the raw surface.

The cause for such wide variations in the morphology and structure of basal-cell cancer is interesting. As basal-cell cancer arises from the deep layers of the epidermis, it is consequently more closely akin to such structures as the sweat and sebaceous glands and hair follicles than would be spinous-cell cancer that springs from the superficial layers of the epidermis. It seems probable that these variations and simulations of gland structure or adamantinomatous cells are reversions due to the closer relation of the basal cell to these glands and hair follicles which are also derived from the deep layer of the epidermis.

It is rather common for spinous-cell cancer, particularly of the more malignant grades, to metastasize in the nearest lymph-nodes; whereas meta-

stasis of basal-cell cancer is exceedingly rare and constitutes a pathological curiosity. A few cases of well-authenticated metastases of basal-cell cancer have been reported by Finnerud (Finnerud, W.: Metastatic Basal-cell Carcinoma of Skin, *J.A.M.A.*, vol. lxxxii, No. 10, pp. 775–778, March 8, 1924), but they are about as rare as the spontaneous healing of cancer, and for purposes of therapy may be disregarded. Finnerud reported from his practice two cases of advanced basal-cell cancer in which there were undoubted metastases in the lymph-nodes of the neck. Both of the patients were operated upon by Phemister. The original growth and the enlarged lymph-nodes examined histologically showed the same type of basal-cell cancer. In the late stages of one case there was very marked cystic formation. Finnerud has searched the literature and finds only five other instances of metastasis of basal-cell carcinoma. The reports of some of these five cases are incomplete and in others the histologic examination was not conclusive. Definite proof of metastasis of basal-cell cancer, according to Finnerud, was given in only one case which was reported by C. F. Beadles (Beadles, C. F.: Rodent Ulcer, *Tr. Path. Soc. London*, vol. xlv, p. 176, 1894).

FIG. 4.—(Case I, Mr. G. K. P.). Photomicrograph of basal cell cancer in this case. The top shows the cauterized surface of the cancer. Though the cauterization was thorough and the cancer cells had not penetrated deeply, the deep layers of cells are still intact, which shows the futility of depending solely upon surface cauterization for a cure of extensive basal cell cancer. (X 155.) (This and the preceding two photographs are from the *Journal of the Am. Med. Asso.*, vol. lxxviii, pp. 412-416, Feb. 11, 1922, in which the preliminary report of this case was made.)

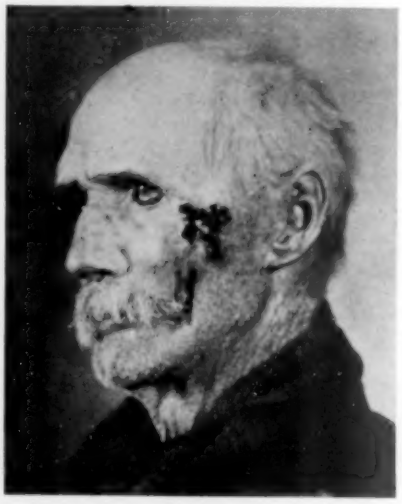

FIG. 5.—(Case III, Mr. W. T. G.). Photograph showing basal cell cancer of the left cheek before operation.

The rarity of metastasis of basal-cell cancer is so conspicuous, and metastasis from spinous-cell cancer, except from the grade 1, according to the classification of Broders, is so common that this extreme difference calls for consideration. Basal-cell cancer usually occurs in the face above the lower lip and is most

often seen around the eyelids and the nose. The temporal region and behind the ear are also occasional sites for it. These same areas are often attacked by spinous-cell cancer. The cells of these two types of cancer are about the same size, the spinous-cell usually appearing larger, and they have access to the same lymphatics and blood-vessels. If the cells of basal-cell cancer have equal opportunity with the cells of spinous-cell cancer for transportation by the lymphatics, the marked difference in the tendency to metastasize can be attributed neither to the size of the cells nor to anatomical differences in the invaded tissue. The real cause for this difference appears to be due to the great resistance of normal tissues to the growth of basal-cell cancer, whereas for the more malignant grades of spinous-cell cancer such resistance either does not exist or is readily overcome. It is probable that during the growth of basal-cell cancer some product is elaborated which breaks down the resistance of the adjacent tissues but does not affect tissues at a distance. In what manner this substance may act is unknown.

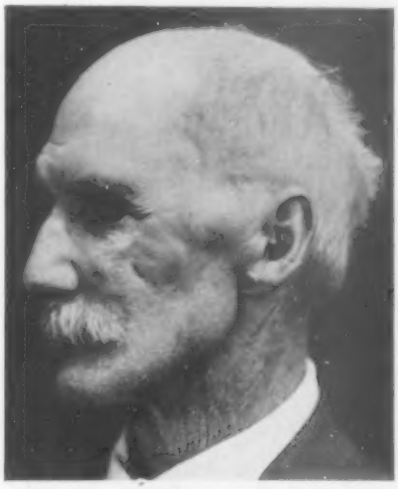

FIG. 6.—(Case III, Mr. W. T. G.). Photograph taken one year and four months after operation. The transplanted flap from the forehead covers the area of excision and seems to be in good condition.

FIG. 7.—(Case III, Mr. W. T. G.). Photograph taken two years and four months after operation, showing recurrence in the cheek to the inner side of the flap, which has gradually encroached upon the margin of the flap. The flap itself, however, is unaffected.

On this hypothesis it seems logical to treat intractable basal-cell cancer by the transplantation of a flap taken at a sufficient distance from the basal-cell cancer to insure that the resistance of the flap to the growth of the basal-cell cancer has not been overcome. This, of course, is only one phase of the operation, but an important phase. Many recurrences after operation for basal-cell cancer are doubtless from the implantation of its cells into the raw surface left by the excision. It is for this reason that treatment with a paste has often been more successful than excision with the knife. The greatest care should be taken to prevent implantation. The surface of the cancer should be well cauterized with the electric cautery and the excision should be made either with the cautery or else with the knife followed immediately by cauterization of the raw surface. If more rapid healing

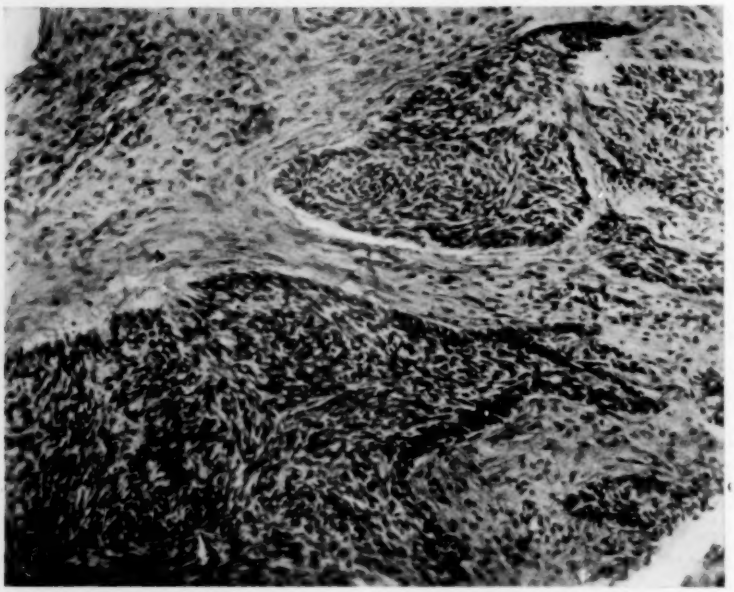

FIG. 9.—(Case IV, Mr. C. B.). Photomicrograph of basal cell cancer. This shows the type of spindle cells commonly found in basal cell cancer. (X 150.)

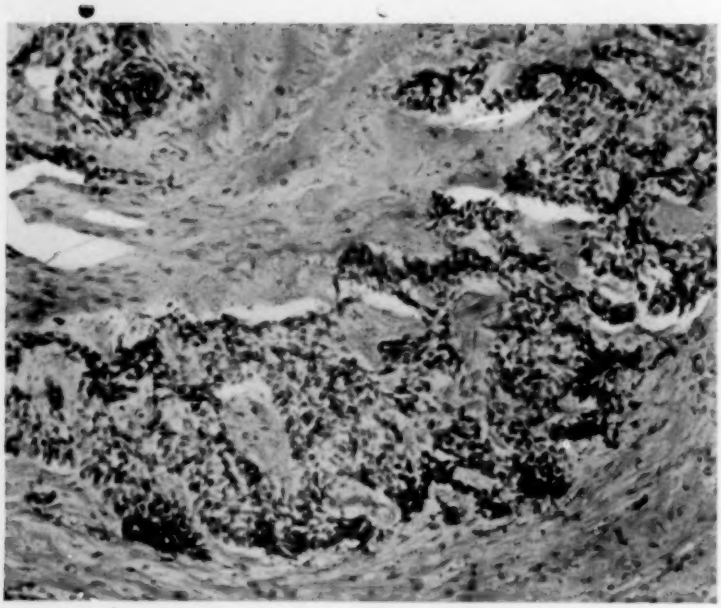

FIG. 8.—(Case III, Mr. W. T. G.). Photomicrograph of basal cell cancer. Note the tendency to formation of acini and cystic cavities. (X 150.)

is desired, the burnt surface can be dissected off with a sharp knife, leaving a wound ready to receive a graft. When it seems inadvisable to excise the burnt surface, it would be well to postpone the transplantation of the graft for a week or two until the cauterized area has formed granulation tissue.

The depth to which the resistance to basal-cell cancer conferred by a flap extends is difficult to determine. The small blood- and lymph-vessels soon form a network of anastomoses between the raw surface of the flap and the raw surface left by excision of the cancer. Tissue juices of the graft and of the wound would seem to communicate freely on the surface of the wound and probably some communication of these tissue juices extends with decreasing freedom to a depth of a half centimetre. At any rate, there has been no recurrence that originated closer to the transplanted distant flap than about a half centimetre.

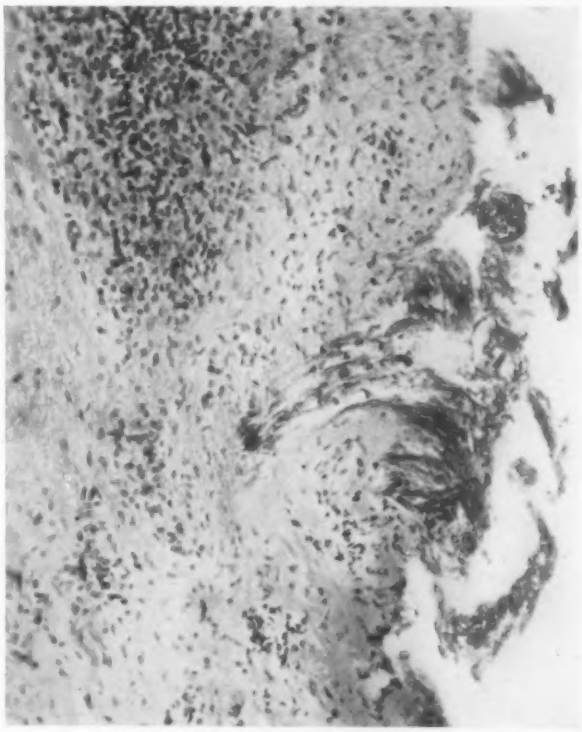

FIG. 10.—(Case V. Mrs. J. O. J.). Photomicrograph of basal cell cancer. The cancer cells which show in the right of the picture are long and filament-like. There is a dense stroma beneath them, and marked leukocytic infiltration. The patient had had extensive röntgenologic treatment. (X 150.)

Basal-cell cancer in the early stage is often very amenable to treatment. Excision with knife, cautery or paste, or treatment by radium or röntgen-ray, is usually effective. In early cases one of these methods or a combination of them should be adopted. There is, however, a small percentage of basal-cell cancers which is not relieved by any of these means. The cancer progresses, spreading in all directions at a rather uniform rate from the surface until intervening tissues are destroyed and the bone is eroded. When the mucous membrane is reached the growth seems to become accelerated. Operation in such cases by the ordinary methods of excision is futile. Radiologic treatment apparently does not benefit. It is these cases that offer a field for the transplantation of distant flaps containing tissue whose resistance has not been impaired by the substance evolved in the growth of the basal-cell cancer.

The reaction of basal-cell cancer to flaps transplanted from a distance greatly differs from the action of spinous-cell cancer on transplanted distant

flaps. For instance, in the case of Mrs. S., who had an extensive spinous-cell carcinoma involving the left ear, transplantation of a flap from the back of the neck and the upper posterior portion of the chest was made to cover the wound left by excision of the cancer. There was a recurrence in the tissues of the auditory canal, and the cancer rapidly involved the centre of the transplanted flap which was over the auditory canal, growing through the flap and spreading to the surrounding structures. In no case where a flap was transplanted from a distance for the cure of basal-cell cancer has there been a recurrence involving the flap or originating in immediate proximity to it, which is in striking contrast to the action of spinous-cell cancer.

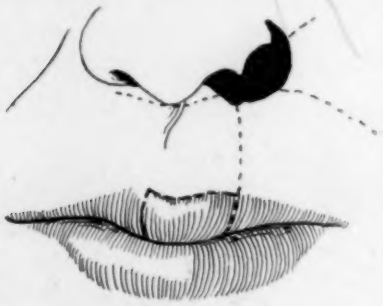

FIG. 11.—(Case VI, Mr. O. A. F.). Drawing showing in black the region of the recurrent basal cell cancer and the lines of incision for its exposure and excision at operation.

Of the ten cases that I have operated upon following this general principle of transplantation of a distant flap, two have already been preliminarily reported.

CASE I.—The first case, Mr. G. K. P., aged forty-nine years, is one of the two cases reported in 1921. He was treated in May and June of 1920, by a series of operations including the excision by cautery of an extensive basal-cell cancer that had destroyed the upper lip and the contiguous part of the upper jaw. (Figs. 1, 2 and 4.) The defect was covered by a flap from the chest with a tubed pedicle, which was raised by dissection in different stages. (Fig. 3.) This flap was eventually applied to the raw surface left by excision of the cancer. About eleven months after operation the patient had a severe attack of cardiac angina of the abdominal type. He gradually recovered from this and resumed his work. In August, 1922, a small ulcerated area appeared on the anterior portion of the left turbinate bone. This was mostly covered with a scab. The ulcer was at no point closer to the transplanted flap than a half inch (1.3 cm.), and appeared to be independent of the original cancer. It was cauterized and excised with scissors and bone forceps, and the raw surface was again cauterized with the electric cautery. Microscopic examination showed basal-cell cancer similar to the original growth. A narrow flap about one and a half inches (3.8 cm.) long was taken from the large transplanted flap, mobilized so that its nourishment would not be interfered with, turned into the nostril, and fastened by two silver wire sutures to the raw surface left by removing the cancer. The bed from which the flap was raised was closed by undermining the margins of the wound and suturing with fine silkworm gut. On February 7, 1924, he died suddenly at a hotel in another city where he was on a business trip. There was no necropsy, but it seems probable that the death was from angina. The patient was very irregular in reporting for examination, and had not been seen by me for about six months before he died. His wife tells me, however, that there was no evidence of the cancer at the time of his death so far as she knew.

FIG. 12.—(Case VI, Mr. O. A. F.). The operation indicated in the previous figure has been completed. The tip of the flap on the left cheek was excised, and after denuding the under surface, the lip is brought over and sutured to this flap. In the third operation the scars resulting from the second operation were incised affording satisfactory exposure. There has been no recurrence since the third operation.

This case is interesting because the basal-cell cancer had existed for fifteen years, had been operated upon by some very prominent surgeons, had been treated by röntgen-ray, and radium had been applied by one who commands large amounts of radium. The cancer, however, had gradually extended, though there would be intervals sometimes of several months after an operation or treatment in which the growth appeared to be checked.

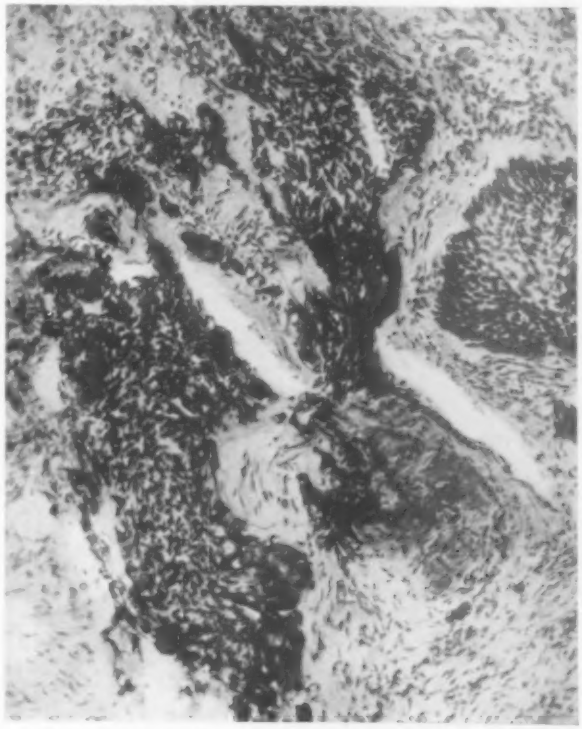

FIG. 13.—(Case VI, Mr. O. A. F.). Photomicrograph of basal cell cancer. This is the common spindle-cell type with a tendency for the cells to be drawn into filaments. This is somewhat the same type of cell as shown in Fig. 9. (X 150.)

CASE II.—The second case, Mrs. D. B. W., operated upon September 28, 1920, was also reported in 1921. She was fifty-five years of age, in bad general condition, with a mitral stenosis. She had a basal-cell cancer that had been growing for twenty years. It began on the nose and progressed until it involved the antrum of Highmore. She, too, had had many treatments with the electric cautery, röntgen-ray and large quantities of radium. In an effort to combine a cosmetic operation with a curative procedure, one flap was turned from the neck and another from the forehead, the epithelial surface of one flap being used to fill the antrum. As a consequence of these misdirected efforts, portions of the wound from which the cancer was excised were not in contact with the raw surface of the flap. It is interesting to note that at these areas the basal-cell cancer recurred, but at no point where the raw surface of the transplanted flap grew to the raw surface left by excision of the cancer was there any recurrence. The cancer recurred particularly beneath the eye along the orbit and in the palate. She died June 25, 1922.

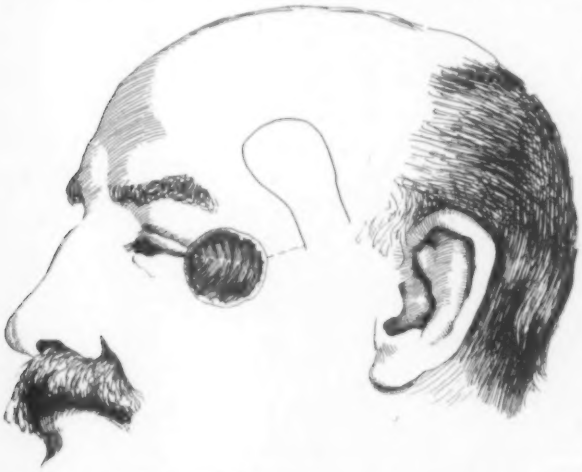

FIG. 14.—(Case VII, Mr. E. W. H.). Drawing showing the excised basal cell cancer with the outline of a flap which was transplanted over this area seven days after the first operation.

Both of these patients were living when their cases were reported in 1921.

The following eight cases have been operated upon since the above two were reported:

CASE III.—Mr. W. T. G., seventy years of age, noticed about 1910, a growth on the left cheek which he first thought was eczema. It gradually extended and in 1917 broke down and formed a large ulcer. The patient was treated without benefit by an advertising cancer-cure charlatan. A skilled röntgenologist then gave extensive röntgenologic therapy which appeared to check the growth, but it did not heal. (Fig. 5.) On December 10, 1921, I excised a basal-cell cancer from the left cheek with the electric cautery, including a small margin of apparently healthy skin. A portion of the malar bone was also removed. A flap from the left frontal region with the base over the zygoma was sutured over the raw surface. The patient made a satisfactory immediate recovery. (Fig. 6.) September 5, 1923, he reported with a recurrence in the cheek to the inner side of the transplanted flap. (Fig. 7.) Under local anæsthesia a superficial recurrence in the skin was cauterized and excised with a knife. Beneath this toward the nose was an infiltrating firm mass which proved to be an extension of the basal-cell cancer. (Fig. 8.) Beneath the flap, however, there was soft normal tissue and no evidence of recurrence. The growth progressed to the margin of the flap, but did not involve it. (Fig. 7.) As it was quite extensive it could not be completely excised and the wound was left open and the patient was treated with deep röntgen-ray therapy by Dr. Fred M. Hodges.

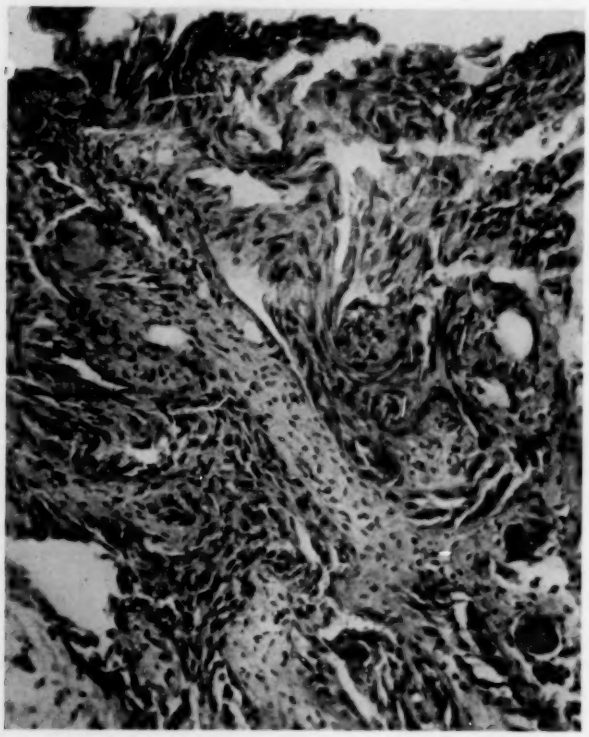

FIG. 15.—(Case VII, Mr. E. W. H.). Photomicrograph of basal cell cancer. The cells are spindle type with many areas in which they are drawn out into filament. The type of cell is somewhat similar to that shown in Figs. 9 and 13, though the cells show more degeneration. There are numerous small cystic cavities not lined with any distinctive cells. These cavities appear to be due to degeneration of the cells and are quite different from those shown in Fig. 18, in which there is distinct acinous formation with a lining of cubical cells. (X 150.)

A letter from him, April 2, 1925, states that the cancer has partly healed in some places but still persists in the inner portion of the left cheek. There is a large fistulous communication with the mouth. The transplanted flap, he reports, has not been involved by the cancer.

CASE IV.—Mr. C. B., aged sixty-one, had noticed a growth about the right ala of the nose in 1912. Various treatments had been applied without benefit. On May 30, 1922, I operated upon him, first excising an ulcerating basal-cell cancer with a knife and then cauterizing the raw surface thoroughly with the electric cautery. (Fig. 9.) During the following June a flap was raised from his forehead in different stages, and was transferred to the raw surface left by excision of the basal-cell cancer. In November, 1922, he returned for further plastic operations, no attempt having been made for cosmetic

effect at first. In a letter from the patient's brother dated April 21, 1925, the patient is reported as being without evidence of recurrence.

CASE V.—Mrs. J. O. J., aged fifty-two years, had a basal-cell carcinoma of the left cheek and lower eyelid which began in 1913. She had been treated by röntgen-ray and by radium, which seemed to retard the growth but did not cure it. There was an involvement of the lower left eyelid and the cheek for a distance of about an inch (2.5 cm.) below the eyelid. She was operated upon May 4, 1923. The ulcerated area was cauterized with the electric cautery and the left lower eyelid, the adjoining portion of the cheek and a portion of the conjunctiva were excised. (Fig. 10.) A flap was taken from the forehead with the base near the left zygoma, and turned over this area. The patient made a satisfactory recovery. When heard from, April 11, 1925, she was well and had no recurrence.

FIG. 16.—(Case VIII, Mrs. A. R. M.). Photograph of patient before operation. Much of the original growth on the nose has healed except at two small points. The cancer is growing along the inner canthus of the left eye and involves the eyeball and both eyelids.

CASE VI.—Mr. O. A. F., aged forty-nine, had at the base of the left ala of the nose a basal-cell cancer which had been present for eighteen months and had been treated by salves and paste. On June 1, 1920, the cancer was cauterized with the Percy cautery and excised with a sharp electric cautery. Superficial portions of the bone were removed with a chisel and rongeur forceps, and the wound was cauterized with the electric cautery and packed with iodoform gauze. No attempt was made to transplant a flap. May 17, 1923, the basal-cell cancer had returned in the floor of the left nostril. The lip was divided with the electric cautery, which exposed an ulcerated area about ¾ inch (2 cm.) in diameter involving the floor of the left nostril, the underlying bone and the adjacent mucosa of the upper lip. The whole area was thoroughly cauterized with the electric cautery and excised. A tongue-like flap was dissected from the left cheek and the right portion of the upper lip was mobilized as much as possible. The columna of the nose and the anterior portion of the septum of the nose were divided. The right portion of the lip was brought into the defect made by removing the ulcer and the quadrilateral tongue-like flap that had previously been made on the left cheek was drawn over. It seemed impracticable to bring over tissue at a further distance from the margin of the wound so that this quadrilateral flap from the cheek, the apex of which had been excised about a half inch (1.3 cm.) from the margin of the wound, was united with the right side of the lip, hoping it would be sufficiently far from the cancer to have an inhibitory effect upon its growth. (Figs. 11 and 12.)

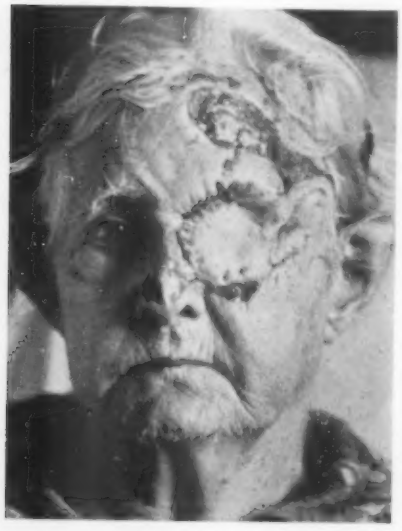

FIG. 17.—(Case VIII, Mrs. A. R. M.). Photograph taken fifteen days after the operation, showing the flap transplanted from the forehead and covering the raw surface made by the excision of the cancer. The cauterized area on the left side of the nose is covered with a scab.

July 22, 1924, he was operated upon for a recurrence. (Fig. 13.) The lip was incised along the lines of the previous plastic operation. The area of recurrence involved the bone of the superior maxilla at the base of the left nostril and along the alveolar process. The incised margins of the lip were lightly cauterized with the electric cautery and the cancer was thoroughly burned. The ulcerated area was excised with a knife, curette and chisel, and the raw surface was again thoroughly cauterized with the electric cautery. This cauterized area was finally removed with a knife and chisel and a flap of fascia and muscle tissue was made from the under surface of the lip on each side, after reflecting the mucosa. These flaps were brought together in the midline and sutured with catgut over cavity from which cancer had been removed. The lip was sutured over this.

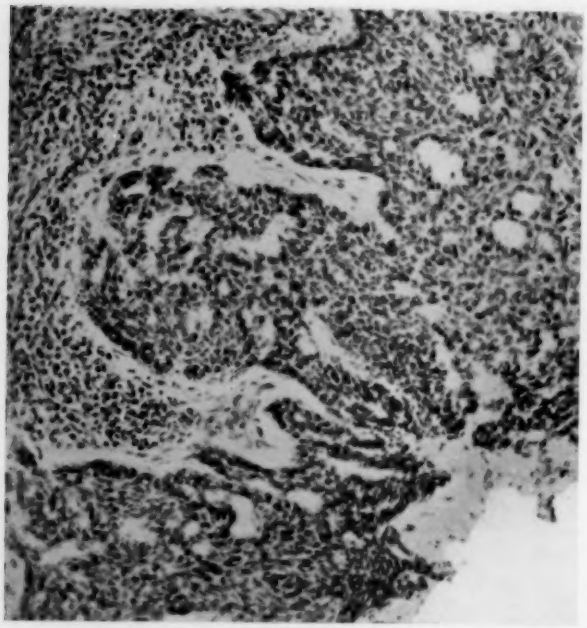

FIG. 18.—(Case VIII, Mrs. A. R. M.). Photomicrograph of basal cell cancer. Note the acini which are abundant throughout the field. These cavities are lined by a cubical epithelium, possibly a reversion to the type of sweat gland. These cavities are quite different from those shown in Fig. 15, and are not due to degeneration of cells. (X 150.)

March 5, 1925, the patient reported some discharge from the nostril. The nostril was contracted and a view of the internal surface of the nose was difficult. He was referred to Dr. E. U. Wallerstein, a rhinologist, who examined the nostril carefully and found a small loose spicule of necrotic bone, which he removed. There appeared to be no evidence of cancer.

CASE VI.—Mr. E. W. H., aged fifty-nine, about a year previous to admission to the hospital, had noticed a small scab-like growth near the outer canthus of the left eye. This spread, and five months later the patient consulted a physician. Röntgenologic therapy was given over a considerable period of time, but without benefit. The growth had elevated, firm margins, and was in close proximity to the outer canthus of the eye. The actually ulcerated area measured about 1¼ inches (3 cm.) in vertical diameter, and about ¾ inch (2 cm.) horizontally. January 24, 1924, the surface of the growth was cauterized with the electric cautery and excised with a knife, and the resulting wound was cauterized with the electric cautery. A flap was outlined with its base at the left zygoma and the apex on the forehead. The base of the flap was not in

FIG. 19.—(Case IX, Mrs. E. Y. M.). Photograph showing basal cell cancer before operation. The larger growth is on the right temporal region. There is also a smaller lesion on the forehead.

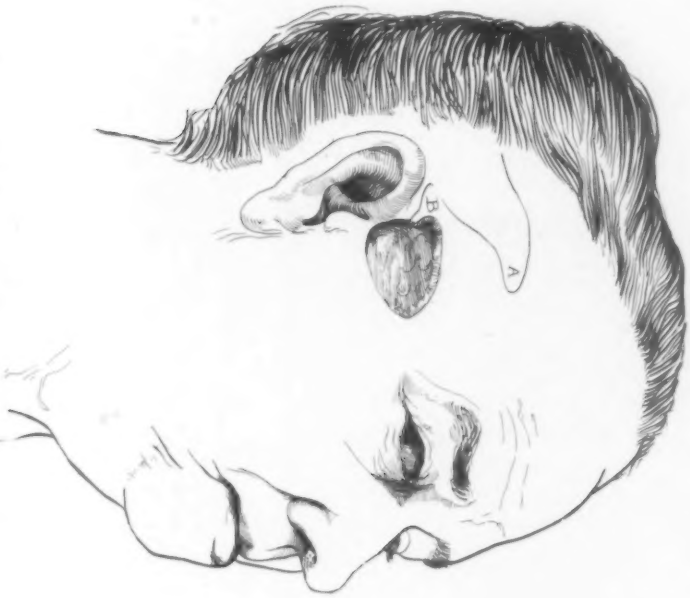

FIG. 20.—(Case IX. Mrs. E. Y. M.). Drawing showing the outline of flap to be transplanted from a distance in order to cover the raw surface left by excision of the basal cell cancer.

FIG. 21.—(Case IX. Mrs. E. Y. M.). Drawing showing the flap outlined in the previous figure transplanted and being sutured in position.

contact with the margin of the excised wound. (Figs. 14 and 15.) The bridge of tissue between the wound and the base of the flap was divided. A week later the flap was turned down and sutured in position. It covered all of the wound satisfactorily, except a small area at the inner extremity, where the eyelid could not be fitted accurately to the flap without undue tension.

May 12, 1924, a small nodule appeared in the left lower eyelid a short distance from the margin of the transplanted flap but not in contact with it. Under local anæsthesia this area was cauterized and then excised. A plaque of radium was also applied. The operation for this recurrence was done by my associate, Dr. A. I. Dobson.

His physician, Dr. J. A. Mood, Sumter, S. C., under date of April 10, 1925, reports there is no evidence of recurrence.

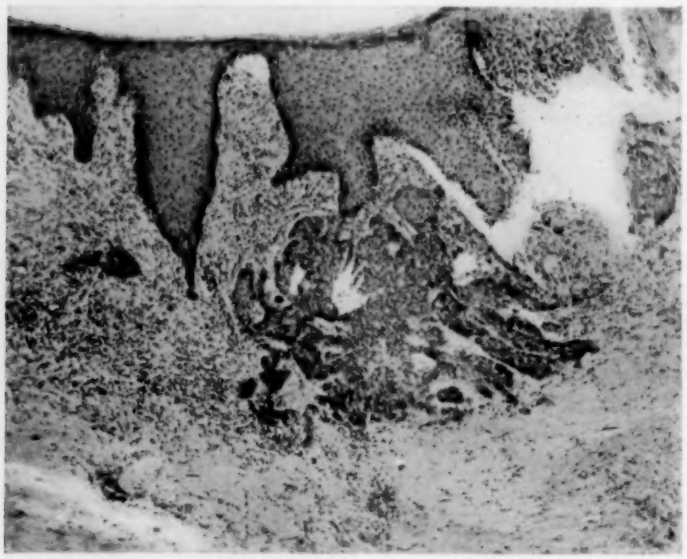

FIG. 22.—(Case IX, Mrs. E. Y. M.). Photomicrograph of basal cell cancer. This was taken near the margin of the ulcer and shows what appears to be basal cell cancer arising from the deep layers of the normal epidermis at the top of the photograph. This is the typical structure of the cancerous growth of the ulcer, but the photograph shows what seems to be a basal cell cancer of independent origin in close proximity to the original growth. (X 70.)

CASE VIII.—Mrs. A. R. M., seventy-seven years of age, had a basal-cell cancer which began on the nose about 1905. In 1920, she received röntgenologic treatment with some benefit. She did not continue the treatment. Much of the ulcerated area over the nose had healed, but the cancer on admission to the hospital, October 17, 1924, involved the inner canthus of the left eye, the adjoining portion of both eyelids and the left eyeball. (Fig. 16.) The patient's general condition was not good. Under local anæsthesia the surface of the growth was thoroughly cauterized with the electric cautery. There was also a small superficial ulcerated area on the left side of the nose near the tip and a still smaller one on the right side of the nose which were also cauterized. The tissues around the inner canthus were dissected from the bone with the electric cautery. An incision was made with the knife along the attachments of the eyelids. The fat and fascia were dissected from the orbit, the optic nerve was divided with scissors, and all of the tissues, including the inner canthus, the eyeball and the eyelids, was removed in one mass. At the site of the lachrymal duct there was a small amount of suspicious tissue left. This was thoroughly burned with the electric cautery. Four days later a flap was dissected from the forehead with the base in the left temporal region, and was sutured over the raw surface. (Figs. 17 and 18.) The wound on the forehead was covered with sterile vaseline. She made a satisfactory recovery. Under date of April 10, 1925, she writes that she is well, with no sign of recurrence.

CASE IX.—Mrs. E. Y. M., aged sixty-five years, had two ulcerated areas of basal-cell cancer, one on the right temporal region just above the zygoma, which was quite extensive, and a small lesion about the middle of the forehead in front of the hairline. The ulcer on the right temporal region had existed for eighteen years. The patient had

been treated by a skilled dermatologist, and röntgenologic therapy had been extensively used by a competent röntgenologist. These treatments had extended over several years and there appeared to be a partial healing at one portion of the growth in the forehead. (Fig. 19.) December 2, 1924, the cancer on the temporal region was cauterized and excised, and a flap was formed from the scalp and turned down over the wound. (Figs. 20, 21, 22 and 23.) The frontal lesion, which was small, was excised with the cautery including the pericranium, and the tissues were brought directly together without an effort to transplant a flap from a distance. The wound in the temporal region over which the flaps were transplanted healed satisfactorily. The wound over the forehead broke down and required a subsequent plastic operation. The breaking down, however, was due to tension of the sutures. The patient reported on April 14, 1925, that there was no evidence of recurrence.

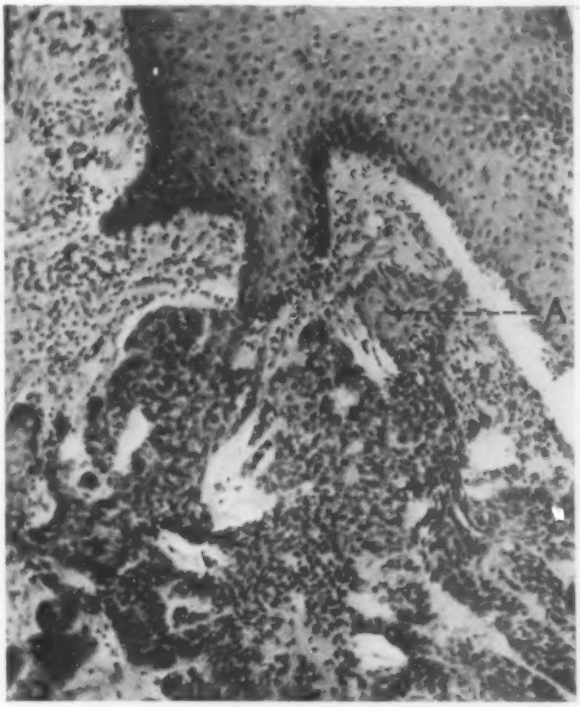

FIG. 23.—(Case IX, Mrs. E. Y. M.). A higher magnification of the field shown in the preceding figure. The cells are mostly oval. There are numerous small cavities, some of which are partially or completely lined with cubical epithelium and simulate acini. Note the apparent origin from the deep layers of the epidermis. At "A" there seems to be the tip of a deep papilla of the epidermis which may have been cut obliquely, making it appear isolated. This apparently isolated area of epithelium seems normal except at the lower portion, where it is continuous with the basal cell cancer. There is similar continuity at the extremity of a papilla from the epidermis shown about the middle of the photomicrograph. (X 150.)

CASE X.—Mr. A. J. E., aged sixty-three, had a rather extensive basal-cell carcinoma on the right side of the forehead between the eyebrow and the hairline. It began in 1909, and had been treated by local applications of pastes and salves. There was a smaller superficial area in the skin in front of the right ear which appeared to be a rather advanced keratosis. December 5, 1924, the region on the forehead was cauterized and excised with the electric cautery. The pericranium, which was adherent to the growth, was also removed. The wound on the forehead was covered by reflecting flaps from each side of the wound. The flaps were so fashioned that the nearest portion of the flap

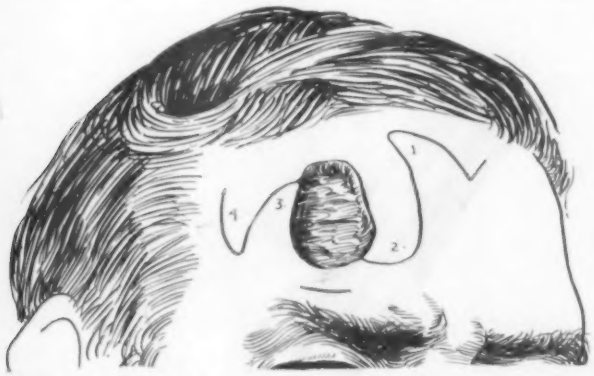

FIG. 24.—(Case X, Mr. A. J. E.). Drawing showing the outline of distant flaps to cover the raw surface left by excision of the basal cell cancer.

to be transplanted was about a half inch (1.3 cm.) from the margin of the wound of the excision. (Figs. 24, 25 and 26.) The keratosis in front of the right ear was well cauterized. A portion of the flaps broke down from tension of the sutures and the wound was later closed by a plastic operation in which a flap was slid over the wound. On April 15, 1925, he reported that there was no evidence of recurrence.

FIG. 25.—(Case X, Mr. A. J. E.). Drawing showing the flaps outlined in the preceding figure partly sutured in position.

SUMMARY

The striking thing about this series of cases is that, though there has been a recurrence in five, in no instance has the recurrence originated along the margin of or within the transplanted tissue when the flap was taken from a distance of an inch or more. In Case VI the transplantation of tissues from a distance was not attempted in the first operation and very imperfectly carried out in the second operation. At the second operation removal of bone from the floor of the nostril left a deep defect, and at the time it seemed better to cover it by approximating the tissues from the margin of the wound, even though the distance was not sufficient, than to transplant a flap which was difficult to fit accurately into this defect. This was an error. Since the third and last operation, on July 22, 1924, in which flaps of fascia and muscular tissue from the lip with their bases along the margin of the wound were sutured together over the excised cancer, there has apparently been no recurrence, though a small piece of dead bone, probably the result of cauterization, was removed.

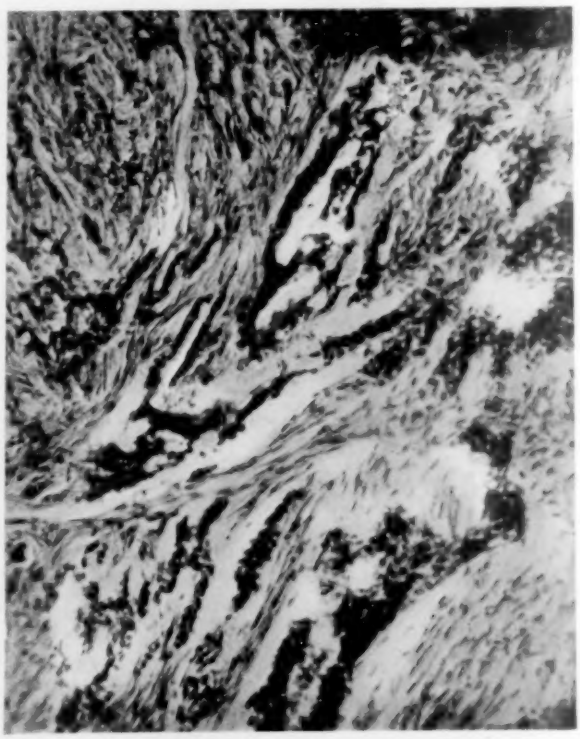

FIG. 26.—(Case X, Mr. A. J. E.). Photomicrograph of basal cell cancer. The cells are small and oval. There is a tendency toward tubular arrangement. (X 150.)

The efforts in Case II to make a cosmetic as well as a curative operation were unfortunate. In no place where the raw surface of the transplanted flap was in contact with the raw surface left by removing the cancer was there a recurrence. The recurrences were where the skin surface of the transplanted flap was apposed to the raw surface left by excision of the cancer, or where no union occurred between apposed raw surfaces. In the other three instances (Cases I, II and VII) the recurrence was not nearer than a quarter of an inch (½ cm.) from the margin of the flap. In one of these, Case VII, the recurrence was in the lower eyelid near a point which the flap did not satisfactorily cover. Since it was excised there has been no further recurrence. In Case III, there is an extensive recurrence in the inner portion of the left cheek. It began a short distance from the margin of the flap. But even though the recurrence has been extensive and still exists, the flap has so far not been affected. On the other hand, in a case of squamous-cell cancer a flap taken some distance from the cancer was quickly involved in the recurrence of the cancer.

Such instances as these appear to indicate that flaps when transplanted from a distance have a distinct inhibitory effect upon basal-cell cancer. Just how deep this inhibitory effect extends it is difficult to say—probably an eighth to a fourth inch (.3 to .6 cm.). This suggests a new principle for the treatment of intractable basal-cell cancers that have not been cured by other measures.

MALIGNANT TUMORS OF THE THYROID*

EPITHELIAL TYPES

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The clinical diagnosis of malignant tumors of the thyroid at a stage sufficiently early to offer a fair prospect of cure by surgical or other therapeutic measures is still an interesting, important, and, as yet, unsolved problem. Fine distinctions as to the type of malignancy present have proved to be very uncertain. It has been the accepted custom in dealing with the clinical aspects of malignant goitre to catalogue the symptoms and signs by which malignancy could be recognized. This procedure, however, is of little practical value since there are few, if any, ultimate cures in the fifty per cent. of cases in which a positive diagnosis is made and verified. Moreover, in the other fifty per cent. of cases there are neither symptoms nor signs sufficiently distinctive to warrant a positive differentiation between a benign and malignant lesion. In view of the foregoing, we shall make no further reference to the clinical aspects of the subject directly. Indirectly, however, it is believed there may be something of interest to the clinician to be derived from a clearer understanding of the pathology of these lesions.

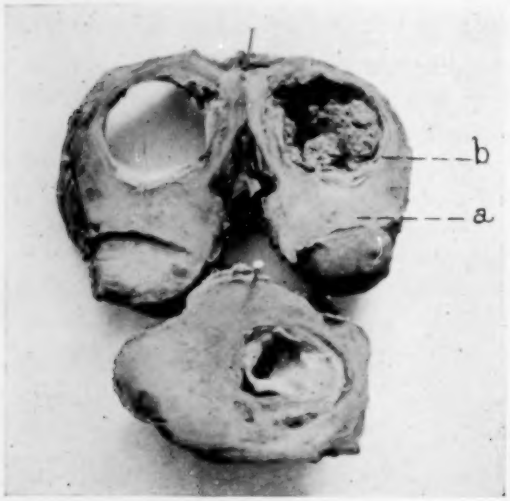

Fig. 1.—S. P., No. 11985. a. Scirrhous carcinoma. b. Degenerating calcareous adenoma.

Those who have had to deal with malignant tumors of the thyroid pathologically know from personal experience some of the difficulties encountered. Those who have sought to solve these difficulties by reference to the literature no doubt have been impressed by the great state of confusion, the endless conflict of authoritative opinion, the hopelessly involved terminology, the lack of satisfactory classification, and the inadequacy of the criteria by which to recognize malignancy in a fairly high percentage of cases.

Perhaps this is not surprising when one considers that the total experience with malignant disease of the thyroid is still comparatively small. A more probable explanation is to be found in the fact that the thyroid has certain peculiarities in regard to its malignant tumors not commonly encountered in

* Read before the Baltimore City Medical Society, April 3, 1925.

other organs or tissues of the body. For example: In no other organ of the body do malignant tumors of epithelial origin proceed so directly on the basis of a preëxisting benign tumor (adenoma) as is the case in the thyroid; in no other organ do malignant epithelial tumors (except chorio-epithelioma) exhibit such a high incidence of metastases through the blood stream; in no other organ does the histological appearance of the cells and tissue, both of the primary carcinoma and of its metastases, so closely resemble benign parent tissue, in such a significant percentage of cases.

In 1923, Joll [1] tabulated from the literature forty-four cases of metastases to bone from thyroids that were said to be, or thought to be, normal or benign. That a primary malignant epithelial tumor, or its metastases, may resemble normal thyroid gland † we emphatically wish to deny. That both the primary tumor and its metastases may resemble benign thyroid lesions, histologically, has been amply attested, and is in accord with our experience.

Another example of the unsatisfactory state of the literature is to be found in this frequently quoted set of incomprehensible contradictions:

The thyroid may be malignant and give metastases that are malignant.
The thyroid may be malignant and give metastases that are benign.
The thyroid may be benign and give metastases that are malignant.
The thyroid may be benign and give metastases that are benign.

Equally perplexing is the great variety of names and combinations of names used to describe individual tumors and types of tumors. Wilson,[2] 1921, gives the following "Principal tumor types" under illustrative cases

Malignant papilloma,
Non-malignant papilloma,
Adenopapilloma,
Adenopapilloma (malignant),
Medullary carcinoma,
Adenomedullary carcinoma,
Scirrhous carcinoma,
Scirrhous adenocarcinoma,
Mixed-cell sarcoma,
Spindle-cell sarcoma,
Alveolar sarcoma suggesting epithelial relationship,
Carcinoma sarcoma,
Round- and giant-cell adeno-sarcoma,
Small round-cell sarcoma,
Adenocarcinoma.
Malignant adenoma,
Proliferating embryonic (fetal) adenoma, malignant,
Proliferating embryonic (fetal) adenoma,
Proliferating embryonic (fetal) adenoma, fibrous degeneration
Non-malignant adenoma,
Non-malignant cystic degenerating adenoma,
Degenerating calcareous adenoma,
Doubtful.

† Those who have reported metastasizing normal thyroids, and metastases resembling normal thyroid, have not made the distinction between normal thyroid gland and adenomatous thyroid tissue.

Considering only epithelial tumors, the two foregoing examples of the confused state of our knowledge are directly or indirectly the natural outcome of the long-standing conflict between what might be termed the morphological and the biological interpretation of the concept carcinoma, as applied to thyroid tumors. According to the morphological view, there must be sufficient variation from the normal in the cells themselves, or their environmental relationships, before the term carcinoma is properly applicable. According to the biological view, the natural history of a tumor, its behavior and effects, are matters of more importance than the size, contour, or tinctorial qualities of cells; recurrence, metastasis, and death of a patient from the disease would be sufficient warrant for use of the term carcinoma, irrespective of histological appearances otherwise. The solution of the problem in this particular instance is to be found in a clear conception of the relationship that exists between adenomata and carcinomata of the thyroid.

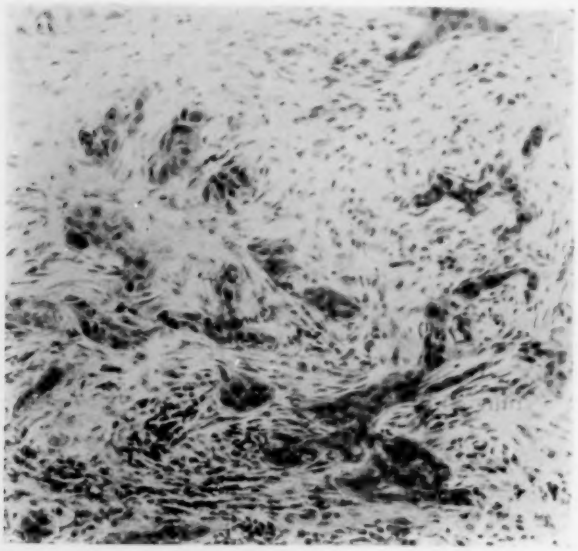

FIG. 2.—Scirrhous carcinoma (Fig. 1-a). (x 150.)

Almost all authors who have undertaken to classify the malignant epithelial tumors of the thyroid pathologically have fallen into the error of trying to separate these tumors into two presumably distinctive groups. One of these groups has been carcinoma, with its various subdivisions, such as medullary, scirrhous, adeno, alveolar, cylindrical-cell, papillary, etc. The other, and somewhat smaller group, has been designated by the use of such terms as malignant adenoma, adenoma with metastasis, metastasizing adenoma, wuchernde struma, metastasizing simple or colloid goitre, and even metastasizing normal thyroid. The difficulty of such a grouping becomes perfectly obvious in those not infrequent instances when every single one of the aforementioned designations is properly applicable to individual tumors, or to a few selected tumors.

In a previous publication [3] we have pointed out that these two supposedly distinct groups are really different phases of the same fundamental pathological process, namely, the transformation of benign to malignant adenoma. This we can show objectively in at least ninety per cent. of all cases. In the remaining ten per cent. we can neither prove nor disprove the adenomatous origin of carcinoma. These facts, together with certain collateral observations

to be mentioned later, have furnished a basis for a conception of malignant epithelial tumors of the thyroid which has been of the greatest practical service from the standpoint of pathological diagnosis, classification, recognition of malignancy, and the adoption of a simple, and at the same time adequate nomenclature. Furthermore, it is believed that there is now available a satisfactory basis for the reconciliation of many of the conflicting views still prevalent.

While this paper deals primarily with malignant epithelial tumors, it may not be amiss to mention sarcomata for the following reasons: (1) The bearing their occurrence may have upon the relative incidence of mesoblastic and epithelial malignancy. (2) Because of the small number of tumors, the malignancy of which is never in doubt, in which it is very difficult to determine positively whether a particular tumor is a sarcoma or a carcinoma. (3) Because of the fact that there are too many cases reported in the literature as sarcomata.

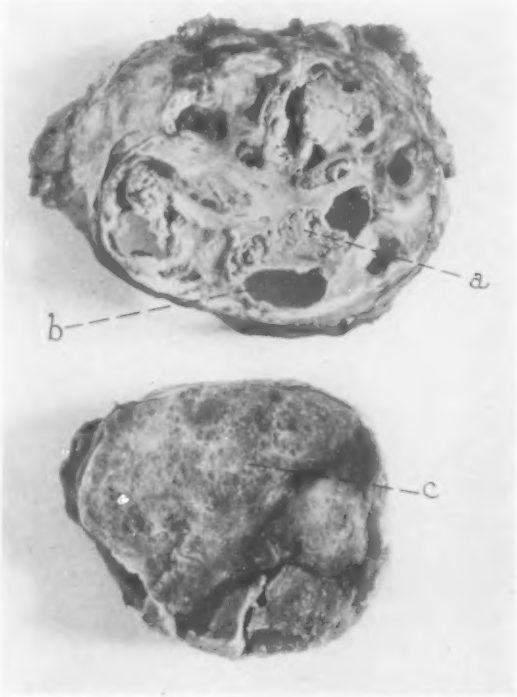

FIG. 3.—S. P., No. 5943. Papillary carcinoma. a. Papillomatous growth. b. Cystic spaces. c. Benign colloid adenoma.

It is interesting to note that Ehrhardt,[4] 1902, reviewed the literature and was able to collect 150 carcinomata to 99 sarcomata. Müller and Speese,[5] 1906, collected 181 carcinomata to 117 sarcomata, including their own cases. In each of these two reviews there were sixty per cent. carcinomata to forty per cent. sarcomata. This is an astonishing incidence of mesoblastic tumors to occur in an organ which is noted for the extraordinary range of physiological and pathological variations of its epithelial elements. Wilson,[2] 1921, reviewed the literature and was able to collect, with the addition of personal communications from American surgeons and the material at the Mayo Clinic, 991 epithelial to 195 mesoblastic malignancies, a proportion of 84 : 16.

About three years ago the writer undertook to review the literature of sarcomata and was thoroughly convinced that up to 1906 a very high percentage of cases reported as sarcomata were typical examples of malignant adenomata.

The basis of this report is the material available at the Lakeside Hospital from 1905 to 1922, and includes the records of 134 patients. In twelve, a clinical diagnosis of malignancy was made, but tissue was not examined. In the 122 tumors examined pathologically there were: 1 parastruma, 10 sarcomata, 3 tumors at present classified as carcinoma-sarcoma, and 108 epithelial tumors. Slightly less than two per cent. of thyroids examined in the laboratory (1915 to 1922—Lakeside Surgical division only) have been malignant. In the following discussion the 108 epithelial tumors only will be considered. Such comparatively rare lesions as primary squamous-cell carcinoma, the glycogen containing para-struma of Kocher, and the struma postbrachialis of Getzowa are expressly excluded since they do not originate from thyroid epithelium and are not cognate to the problem under discussion.

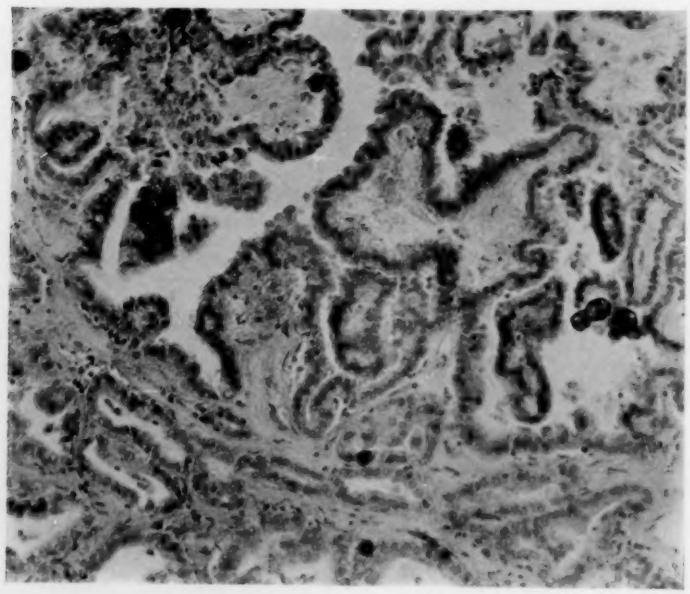

FIG. 4.—Papillary carcinoma (Fig. 3-a). (x 150.)

It is our purpose to divide these 108 epithelial tumors into groups sufficiently distinctive to be worthy of recognition as types, pathologically; to apply an appropriate designation to each type; and, finally, to submit a basis for the differentiation of benign and malignant adenomata. On the basis of gross and microscopic anatomy, the 108 epithelial tumors fall readily into the types mentioned on p. 6. It is to be emphasized that all of these tumors, in the past, have been

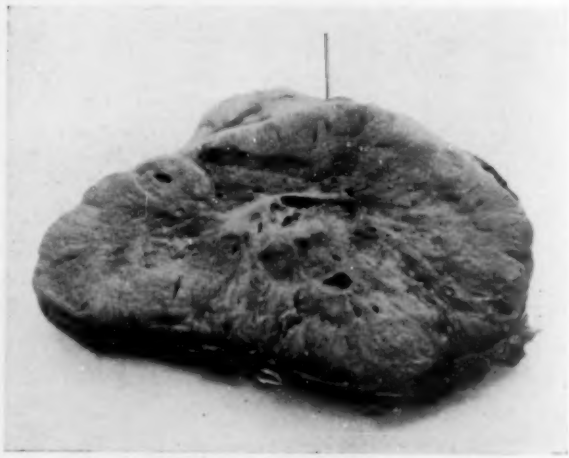

FIG. 5.—S. P., No. 10937. Carcinoma, malignant adenoma type.

diagnosed and considered, by the writer and others, to be malignant, chiefly on histological grounds.

2 Scirrhous carcinomata.
8 Papillary adenocarcinomata,
55 Carcinomata of malignant adenoma type,
43 Adenomata formerly considered malignant, now classed as benign.

Scirrhous Carcinomata.—The tumors included in this group conform to the type so well described by Billroth,[6] 1888, and are not to be confused with malignant adenomata in which there may be areas of dense fibrous tissue, or scar containing compressed epithelial cells arranged in strands or small islands. These lesions are exactly comparable to similar tumors in other organs and present no pathological problem peculiar to the thyroid. They are easily diagnosed and classified from their gross and microscopic characteristics. According to Billroth, they so closely resemble scirrhus of breast as to require no detailed description.

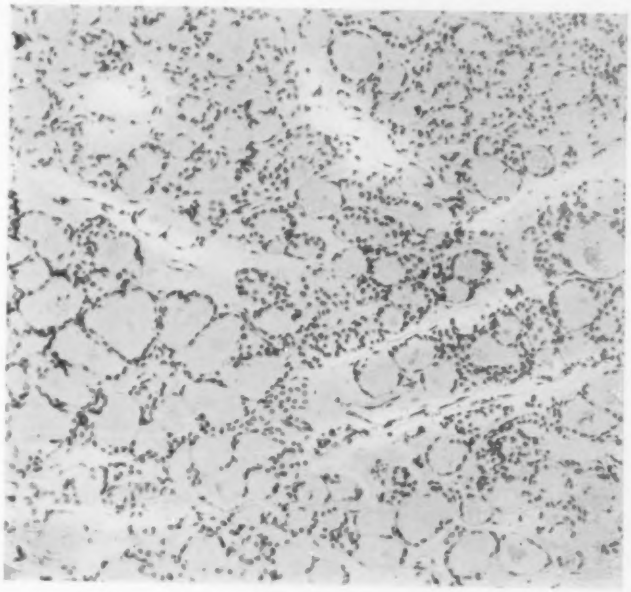

FIG. 6.—Uninvolved thyroid surrounding the malignant adenoma (Fig. 5). (x 150.)

In this group of cases (Figs. 1–2) the thyroid is usually not greatly enlarged, the tumor is not encapsulated, it destroys the affected thyroid, invades surrounding tissue, especially the larynx and trachea, and sometimes the œsophagus. It spreads by direct extension and metastasis to neighboring lymph-nodes. The tumor is hard, fibrous, adherent, immovable, and on section is uniform in consistency and structure. The only lesion with which these tumors can be confused grossly is chronic thyroiditis of the Riedel struma type, or perhaps spindle-cell sarcomata. Microscopically, there is everywhere a great preponderance of fibrous tissue in which are distributed the small masses, cords, or strands of epithelial cells. By the time the patient seeks relief the clinical diagnosis is usually positive, or at least suspected. At operation the surgeon does not remain long in doubt. The tumor cannot be removed without the sacrifice of vitally important structures, hence there are no clinical cures.

This is the one type of carcinoma which we have not been able to associate

definitely with adenoma as regards origin, although the thyroid was adenomatous in each case. So far as our limited experience goes, these tumors do not invade blood-vessels. This is in striking contrast to malignant adenomata, and is in accord with the observation that metastases to distant organs rarely occurs.

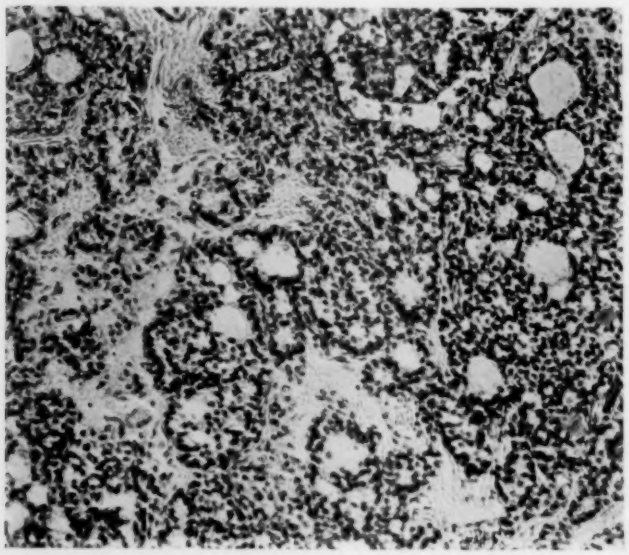

FIG. 7.—Adenomatous or adeno-carcinomatous area in the tumor shown in Fig. 5. (x 150.)

Papillary Adeno-carcinomata.—At the outset it may be stated that a distinction is made between those tumors which grossly and microscopically are made up of papillomatous growths (Figs. 3–4), usually in connection with a cyst, and those solid adenomata in which there may be areas of papilliferous tissue, microscopically but not grossly, somewhat similar to the type of change seen in thyroids from exophthalmic goitre patients. The former only are classified as papillary carcinomata; the latter are classed as malignant adenomata. Metastasis from the former is chiefly through the lymphatics, while metastasis from the latter is primarily through the blood stream, and through the blood stream only as long as the original tumor is still within its own proper capsule. The former exhibit a low order of malignancy, while

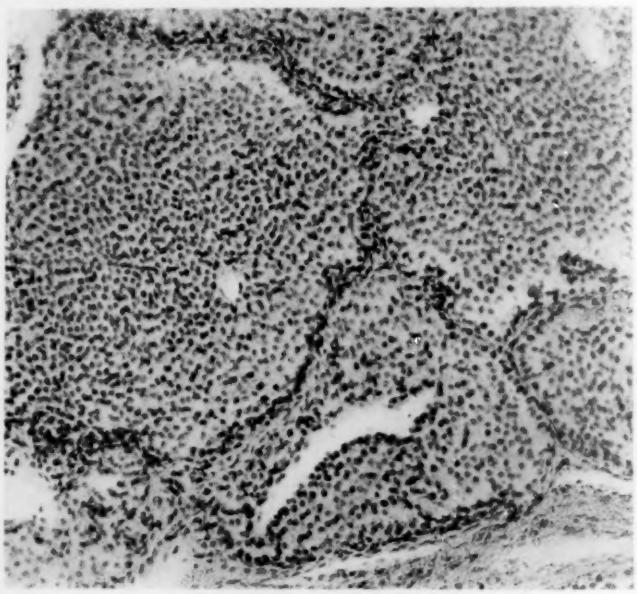

FIG. 8.—Medullary carcinomatous area in the tumor shown in Fig. 5. (x 150.)

the latter, as a class, are highly malignant. For the foregoing reasons, it is important to preserve the distinction between these two types of lesions.

Of eight cases included in this group, six originated in preëxisting adenomata. In the other two cases we can neither prove nor disprove adenomatous origin, although the thyroid was adenomatous in each case. The six cases originating in adenomata were cystic and definitely encapsulated, although the capsule was grossly or microscopically invaded in each case. The two cases in which we can neither prove nor disprove adenomatous origin were small lesions not more than 1 cm. in diameter, solid, non-encapsulated, and made up microscopically of adeno-papilliferous tissue.

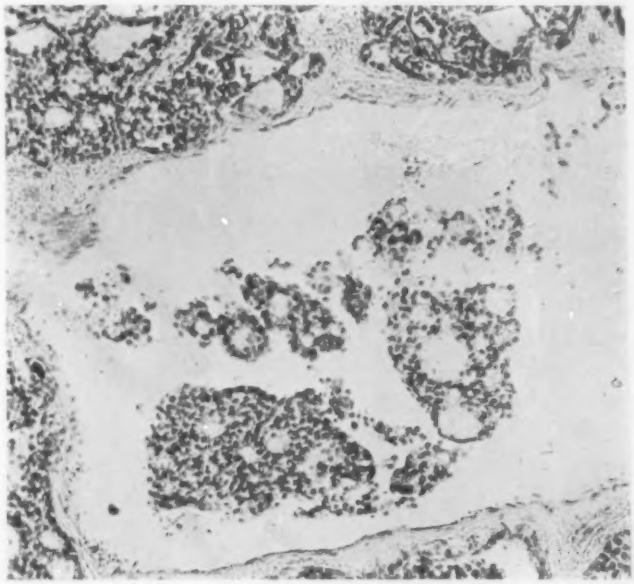

FIG. 9.—Adenomatous tissue within a vein of the tumor shown in Fig. 5. (× 150.)

Possibly in the future, as a result of further experience, it may be deemed appropriate to separate the eight tumors under discussion into two distinct groups, but for present purposes they will be considered together.

Pathologically, the malignancy of these tumors is evidenced by local invasion, grossly or microscopically, of the capsule, surrounding thyroid or neighboring structures, and metastasis to regional lymph-glands. Metastasis to distant organs has not been observed, and this is in accord with the fact that we have been unable to demonstrate invasion of the blood-vessels in any case.

The pathological diagnosis of carcinoma in this group of cases rests on the demonstration of local invasion, and not on the character of the cells primarily.

From the standpoint of treatment and prognosis, this is the most favorable group of carcinomata of the thyroid. In two cases small solid tumors, not exceeding 1 cm. in diameter, were well confined within the lateral lobes. From their size and position, they could not possibly have caused any clinical symptoms, and were discovered in the course of routine examination of supposedly benign goitres removed by operation. These patients are living and well eleven and eight years, respectively, after operation. Of the six cystic papillomatous tumors, two were diagnosed, or suspected as malignant

before operation. The tumors were removed in five cases; in the sixth case exploratory operation was done, but the tumor could not be removed, and only a small piece of tissue was excised for microscopic examination. This patient died a few weeks after discharge from the hospital and is the only recorded death in this group of eight cases. In the five cases in which the tumor was removed, the operation performed was usually of such a nature as to offer little or no prospect of cure in any other type of malignant tumor of the thyroid. That is to say, the cystic tumor was ruptured, cut into, or removed in pieces, and in some cases incompletely removed. In spite of this circumstance and later apparent recurrence (in some cases), the tumor has shown a remarkable tendency to remain localized in the neck. Their further progress has seemed to be held well in check by means of X-ray and radium therapy. The ultimate outcome in those patients with obvious recurrence is a matter for the future.

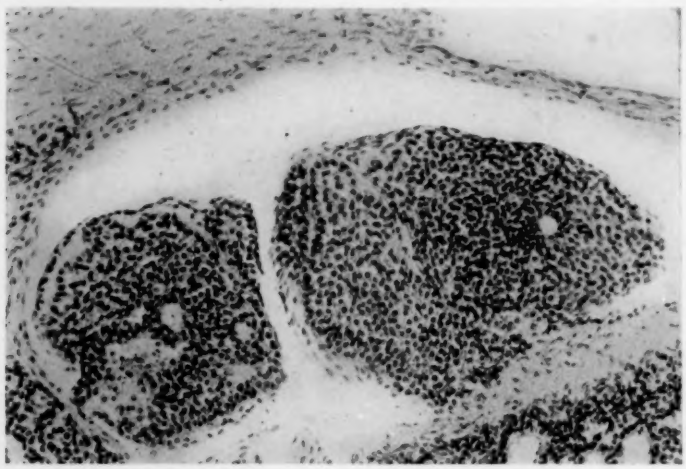

FIG. 10.—Cancer tissue within vein of tumor shown in Fig. 5. (x 150.)

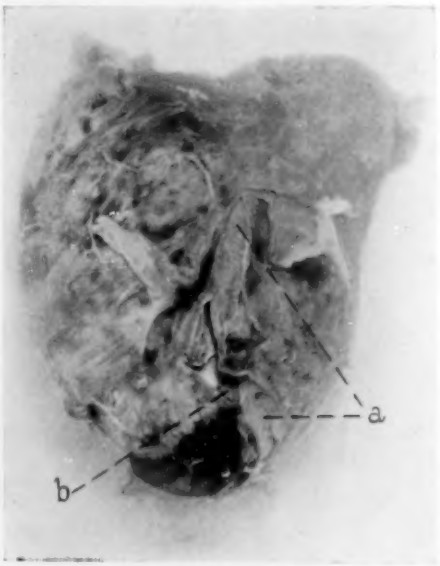

FIG. 11.—S. P., No. 10777. Malignant adenoma. The opened thyroid vein (a) shows an area of gross erosion (b) of vein wall.

Malignant Adenomata.—It is to be understood that the tumors in this group are considered to be carcinomata, and that the term malignant adenoma is used to designate a type of thyroid carcinoma. The only carcinomata of the thyroid originating in adenomata not included in this group are six papillary carcinomata. The reasons for their exclusion have been noted above. Malignant adenomata constitute about eighty-five per cent. of all carcinomata of the thyroid, and, therefore, are the most important type of malignancy.

In this group of 55 malignant adenomata (Figs. 5–12) we find every conceivable form, stage and degree in the growth, differentiation, and degeneration of fetal, intermediate or mixed and colloid adenoma. Furthermore, we find all grades of transition of the original adenoma into every supposed type and combination of carcinoma mentioned in the literature, except pure papillary and pure scirrhous carcinoma. For this reason there is an endless variety of histological pictures to be encountered in the group and in individual tumors. The histo-pathological character of the tumors when seen at operation or autopsy depends upon a number of factors, among which may be mentioned: The character and condition of the original adenoma; the duration of the lesion; the rate of growth; the character and degree of reaction simultaneously or subsequently initiated in the supporting stroma, scar, or capsule; the blood supply; and the degenerative changes that have taken place. There may be, and doubtless are, other factors difficult or impossible to evaluate. It is further to be noted that in a large majority of cases the ultimate histological picture is a mixed and not a pure type. That is to say, that in a given single tumor there

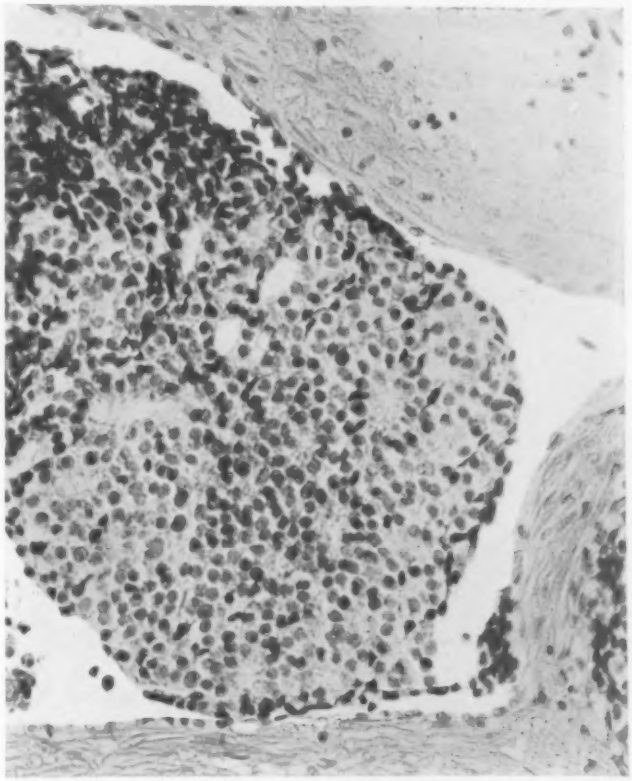

FIG. 12.—Thrombus in thyroid vein of malignant adenoma shown in Fig. 11. (x 300.)

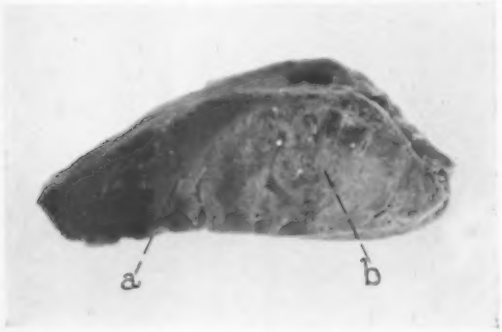

FIG. 13.—S. P., No. 12093. Benign adenoma, formerly considered malignant. a. Hemorrhagic fetal adenomatous area. b. A more cellular area.

may be areas of tissue having the microscopic appearance of pure fetal adenoma, more or less intimately admixed with areas of medullary carcinoma, adenocarcinoma, scirrhous carcinoma, papilliferous carcinoma, spindle-cell carcinoma, carcinoma resembling sarcoma, wuchernde struma, and all the other names that have been applied to adenomata that give recurrences or metastases, and result in the death of a patient. In short, one may find microscopically in these tumors any and every variety of benign, malignant, or metastasizing epithelial growth, except normal thyroid gland.

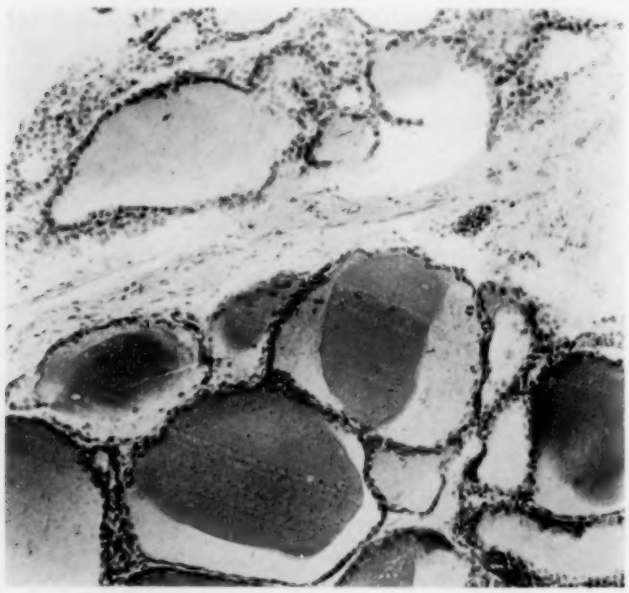

FIG. 14.—The uninvolved thyroid surrounding the tumor shown in Fig. 13. (x 150.)

In view of the foregoing, it seems totally illogical to attempt to separate the essential entity malignant adenoma into a number of artificial groups, supposedly types, which, in themselves, with rare exceptions, are not pure lesions. At least, it is certainly impracticable, and has been responsible for much of the confusion that exists.

As for the recognition of the type of malignant tumor under discussion, one may, for the sake of emphasis, utilize this simple but effective rule: If the tumor is not grossly and microscopically papillomatous (Figs. 3–4, and if it is not grossly and microscopically scirrhous carcinoma (Figs. 1–2), then it is malignant adenoma (Figs. 5–12). However, one must admit the possibility of a carcinoma of the thyroid not originating in an adenoma, and neither of the scirrhous nor papillary type. In view of all the facts now available, the probability of such an occurrence must be extremely small.

Since carcinomata of the malignant adenoma type originate in a pre-existing benign tumor (adenoma), they are always, in the beginning, encapsulated lesions. When tumors of this type have penetrated or perforated their capsule, they may spread by direct extension to surrounding tissues, or through the lymphatics to regional lymph-nodes. The clinical recognition of involved lymph-nodes may be taken as an indication that the primary tumor was not encapsulated, or that the capsule has been penetrated or perforated.

We have found no exceptions to this rule. As long as these tumors are confined within their own proper capsules there is no dissemination through the lymphatics.

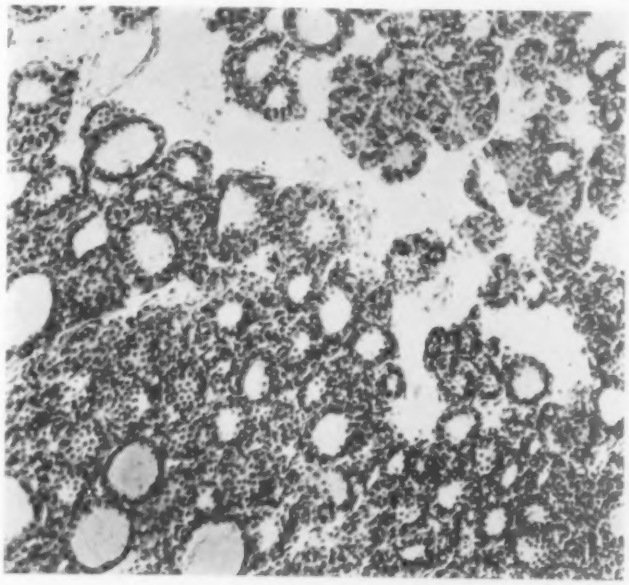

FIG. 15.—From the hemorrhagic area (Fig. 13-a) showing fetal adenoma. (x 150.)

The chief mode of metastasis from malignant adenomata is through the blood stream, with or without intact capsule. Division, during operation, of thrombosed thyroid veins accounts for local recurrence in the neck after what seems to be complete and satisfactory extirpation of tumors well encapsulated. Invasion of blood-vessels (Figs. 9–12) also accounts for distant metastases from tumors causing no clinical symptoms or signs other than swelling in the neck. Indeed, in some instances there has been not even clinical enlargement of the thyroid, and yet the patients have died of metastases.

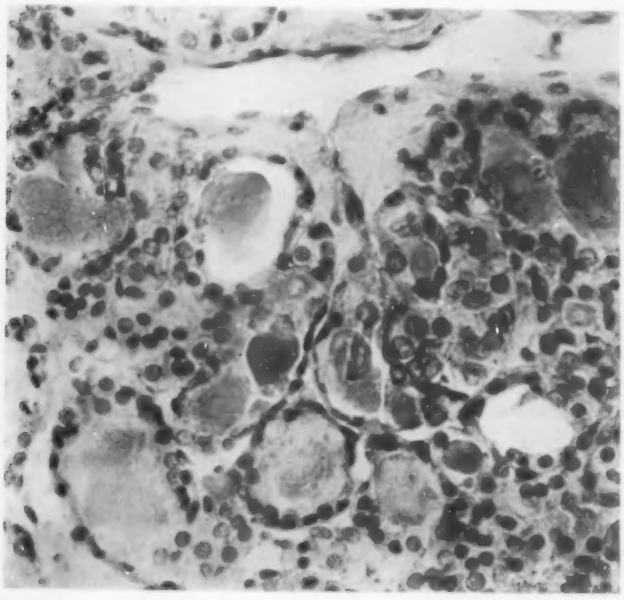

FIG. 16.—From the cellular portion (b) of the benign adenoma shown in Fig. 13. Histologically similar to many adenomata known to be malignant. (x 300.)

Differentiation of Benign and Malignant Adenomata.—In a previous publication[3] the writer has set forth the conclusion that the histological appearance of cells and tissue is not a reliable basis for the

differentiation of benign and malignant adenomata.‡ At the same time it was proposed that invasion of blood-vessels be utilized as the most reliable means of making the distinction. These conclusions were based on the following observations: In no case in our experience in which there was what might be termed histological cancer present, recurrence of the tumor after operation, metastasis, or death of the patient as a result of the tumor, have we failed to demonstrate invasion of the blood-vessels in the original tumor, with the exception of papillary and scirrhous carcinomata, which together constitute

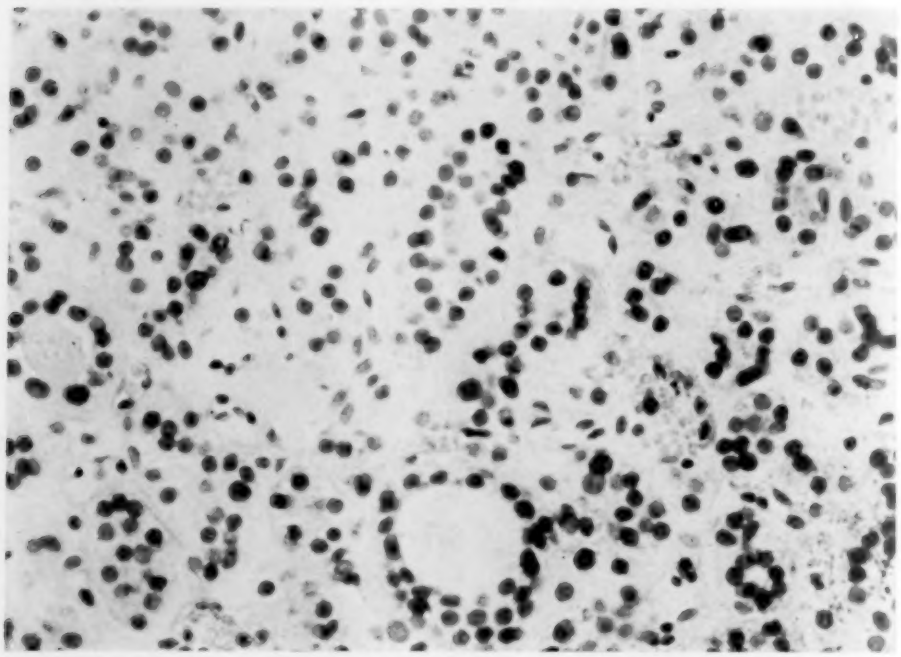

FIG. 17.—Photomicrograph from a benign adenoma, for comparison with Fig. 18. (x 300.) See foot-note below.

about fifteen per cent. of the total. In these two types of tumors invasion of the blood-vessels has been as conspicuously absent as it has been constantly

‡ Figures 17 and 18 are practically identical histological pictures. Figure 17 is from a primary benign adenoma removed from a woman aged thirty, who presented no clinical operative nor pathological evidence of malignancy. This patient is in good health ten years after operation. Figure 18 is from a metastasis in the clavicle of a woman aged thirty-five, whose only complaint was goitre. There was no clinical or operative evidence of malignancy. The primary, large, well-encapsulated adenoma was removed in 1912. Six months later the patient returned with tumor of right clavicle, which was resected. She died five-and-one-half years after the primary operation from metastases in pelvis and femur, without recurrence in the neck or at the site of the resected clavicle. Either picture could be used to represent the other patient's lesion, histologically, and there would be no possible way of knowing which patient would be cured and which would not, on this basis alone. The original sections of the tumor of the second patient were reviewed several years later and tumor tissue was found within the blood-vessels. This phenomenon was not appreciated by the writer in 1912.

present in all other carcinomata. On the other hand, in no case of adenoma in which we have failed to demonstrate invasion of the blood-vessels has there been any clinical evidence of malignancy after operation in any of the patients traced, irrespective of the microscopic appearance of the tumor.

On the basis of the foregoing observations, 43 tumors formerly considered to be malignant adenomata, chiefly on histological grounds, have been withdrawn from the list of malignant tumors and are now classed as benign (Figs. 13–16). When it is recalled that the histological appearances of many

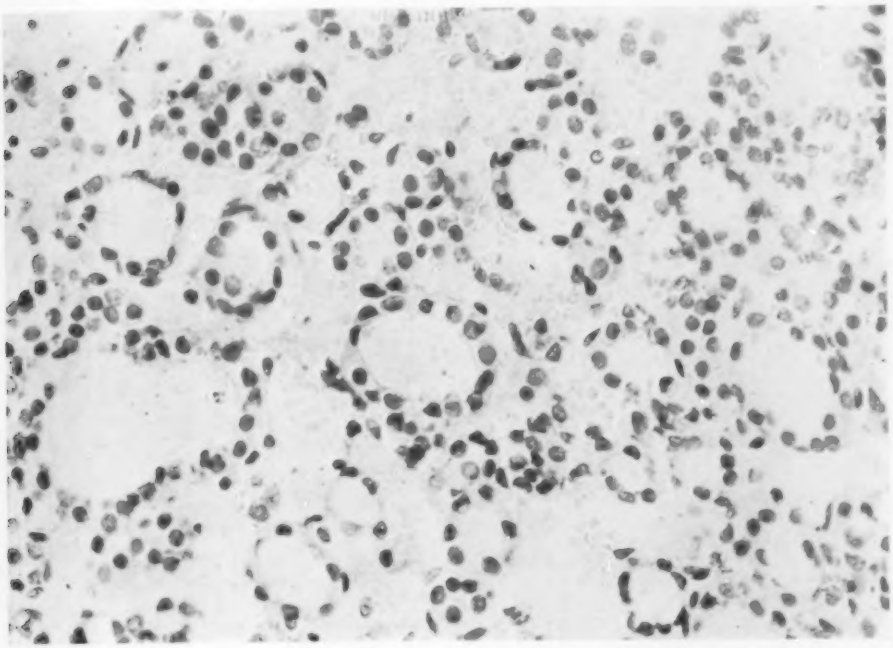

FIG. 18.—Photomicrograph from a metastatic tumor in clavicle, for comparison with the benign adenoma Fig. 17. (x 300.) See foot-note page 42.

of these tumors, now classed as benign, can be exactly duplicated in a number of the 55 adenomata known to be malignant; and further, when it is recalled that in some of the 55 malignant adenomata malignancy cannot be reliably diagnosed on the basis of histological appearances alone, the possible importance of invasion of the blood-vessels as the determining factor in arriving at a diagnosis is apparent, and its importance in prognosis is obvious.

It is not to be supposed that this most constant single indication of thyroid epithelial malignancy will be accurate in 100 per cent. of cases, since serial sections of the primary tumor are not made. Accepting a reasonable number of mistakes in pathological diagnosis, the percentage of errors will still be far less than may be expected from any other criterion that has been proposed.

We claim no originality for the observation that carcinomata of the thyroid frequently invade the blood stream and metastasize by this route. We are unaware, however, that there has been a systematic attempt made to

determine the incidence of invasion of the blood-vessels in a series of cases, to recognize types of lesions in which one may or may not expect to find invasion of the blood-vessels, nor to utilize invasion of blood-vessels as a means of differentiation of benign and malignant adenomata.

The recognition of invasion of blood-vessels is not difficult. Four grades may be noted: (1) Gross thrombosis (Fig. 12); (2) gross erosion (Fig. 11); (3) the finding of tumor tissue or tumor cells within the lumena of blood-vessels microscopically (Fig. 9), and (4) erosion of blood-vessel walls microscopically (Fig. 10). Artefacts are, of course, to be excluded. Examination of the thyroid veins and the veins of the capsule of the tumor will disclose gross thrombosis and gross erosion when present. When not advanced to the degree of gross lesion, a few blocks of tissue through the capsule and from any suspicious area or areas within the tumor will usually suffice for the demonstration of tumor tissue within the veins and erosion of the vein walls microscopically.

The ultimate value of invasion of blood-vessels as an indication of malignancy of thyroid epithelial tumors, and particularly its value as a means of distinguishing between benign and malignant adenoma, is a matter for the future, but on the basis of our experience to date it seems worthy of considerable confidence.

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TUMORS OF THE MALE BREAST*

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of Chicago, Ill.

Though tumors of the male breast may seem to occur rarely, they furnish at least 1 per cent. of the number of all breast tumors which afflict both sexes. A few points of peculiarity of the male breast tumors are worthy of notation on account of the infrequent discussion of these lesions. The male breast may be the site of any pathology which is ever found in the female breast, although the functional use in the two sexes is so vastly different. It might be expected that the rudimentary and non-functioning character of the male breast would lead to its rare involvement in tumor changes, but like other vestigial organs it does undergo untoward mutations and there may be valid argument advanced to prove that the breast either does or does not suffer from tumor on account of its structure.

Predisposing Causes Including Trauma.—The predisposing causes of male breast tumors are obscure. A non-functioning gland is not subject to the hypertrophic and regressive changes incident to lactation nor to the traumata of nursing. Other traumata due mainly to occupation have an influence, as shoemaking or any similar special trade which causes repeated rubbing or pressure over the breast area during the labor. The influence of trauma cannot be definitely analyzed however. If cancer follows one trauma, the hæmatoma reaction may set up sufficient irritation to inaugurate the tumor-forming process. The effect of chronic irritation from occupation pressure or the pressure of clothing may be easier to appreciate. Certainly these irritations will lead to a rapid development of latent cancer.

As an example of chronic irritation, Rodman mentioned one man suffering from breast cancer who constantly had rested his shovel handle against his breast. (Rodman: *Diseases of the Breast*, P. Blakiston's Son and Co., Phila., 1908, page 182). Examples of male breast tumor following a single trauma are rare. A man struck by a horse's bit, with a resulting bruise which slowly disappeared, had within one month a definite freely movable unattached cystic tumor following in the breast just above the right nipple. The skin over this tumor was discolored, in the centre was a bulla, but no ulceration. Griffith who reported this case (*The Lancet*, vol. i, p. 22, January 6, 1923) described a hard nodular mass 1½ inches in diameter adherent to the skin, but not to the muscle, with no axillary or cervical adenopathy. A radical operation was performed, removing the breast and underlying muscle, but not the axillary lymph-nodes. The tumor was macroscopically encapsulated and did not invade the breast tissue, nor the skin stretched over it. The cut section showed a white caseous degenerating mass which histologically proved to be endothelioma, the masses of endothelial cells

* Read before the American Surgical Association, May 5, 1925.

fading into hyaline degeneration with some giant cells present. Murphy (*Surg. Clinics of John B. Murphy*, vol. iii, pp. 569–70, 1914) operated upon a man with carcinoma of the right breast who three months before had been struck there by a bottle thrown from a distance of 10 feet. The breast was immediately swollen and red, but in a week all symptoms disappeared, only to return in three weeks, when a lump developed on the outer side of the nipple. At operation a tumor the size of a pigeon's egg was removed. It was not fixed to the other tissues nor accompanied by nipple retraction, skin pitting or enlargement of the axillary lymph-nodes. Manger in 71 collected cases in men found a preceding trauma in 25, Yamamoto in 257 cases found traumatic history in 61 — over 23 per cent. Ten per cent. of his patients gave an hereditary cancer history

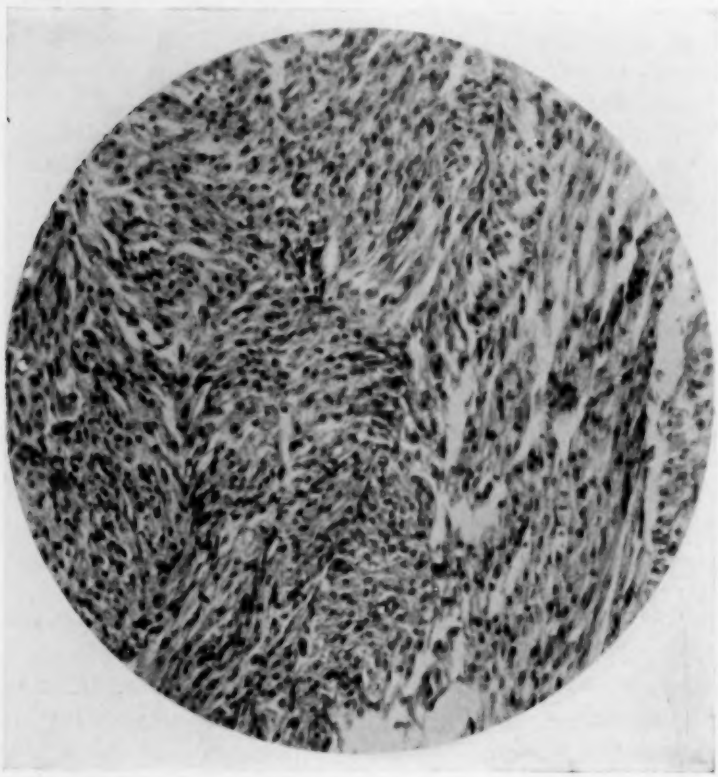

FIG. 1.—Photomicrograph of the breast fibro-sarcoma of patient No. 1. The irregular array of the spindle cells and the lack of stroma are clearly distinguished.

Age.—The age at which male breast tumors are found has wide variation. Lunn reports (*Trans. Path. Soc. of London*, vol. xlviii) mammary cancer in a man aged ninety-one years. Simmons (*J. A. M. A.*, vol. lxviii, p. 1899, June 12, 1917) had as patient a boy aged thirteen years, 121 pounds in weight, who was struck on the right breast by a baseball bat a year before being examined. He noticed burning and stinging in that breast followed in a few months by swelling and tenderness. The only family history of carcinoma was in an aunt aged thirty-five, who had an adenocarcinoma of the uterus. The entire breast and surrounding fatty tissues were removed. No axillary involvement was found, but a microscopic diagnosis of a medullary adenocarcinoma was made. Bryan reported a similar case in a boy of fourteen years eight months, and Thompson (*Brit. Med. Jour.*, 1908, vol. ii,

p. 502) one in a boy of fifteen years. In 1897, Blodgett (*Boston M. and S. J.*, vol. cxxxvi, p. 611, June 17, 1897) reported a breast tumor in a boy of twelve. This was situated below the left nipple, attached to it, and with an appreciable swelling. The nipple was slightly reddened and harder than the opposite nipple. The tumor increased in size in a few months. It was removed and the histological section showed carcinoma invading all the glandular tissue of the breast. There was no recurrence up to five years afterwards. Moore and Coley and Benet (*J. S. Carolina M. A.*, vol. xvi, p. 245, Oct., 1920) record carcinoma in boys aged twelve and nineteen years, respectively. Sir D'Arcy Power found in the breast of a three-year-old boy a multilocular cyst which grew to the size of an orange.

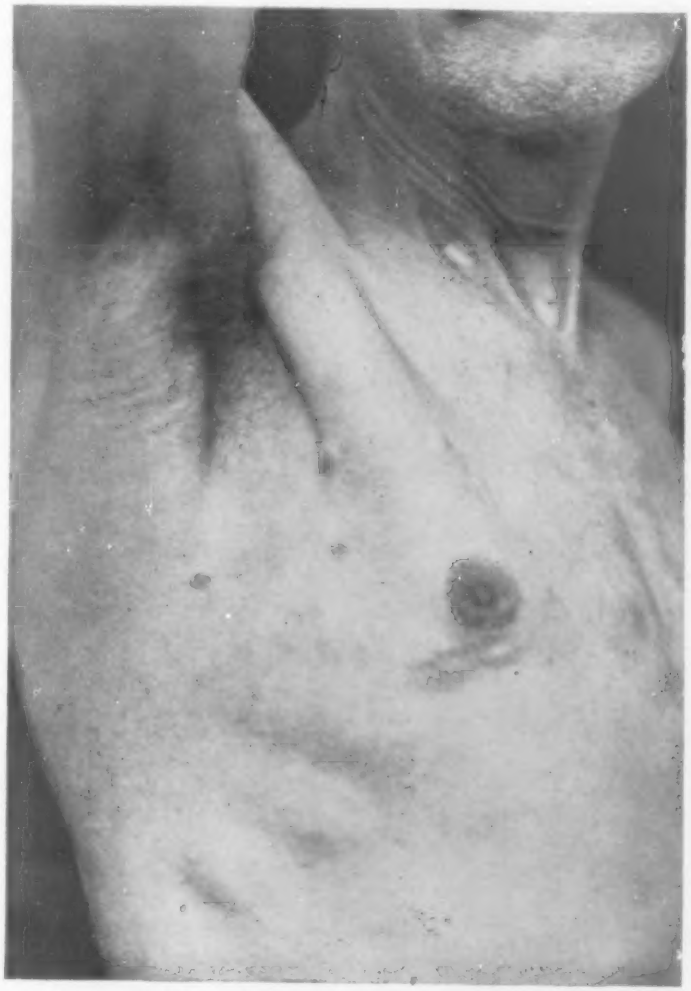

FIG. 2.—Photograph of the involved breast and axillary region of patient No. 2. Beneath the nipple is seen the slightly bulging elongated carcinoma spreading upward into the areola. Scattered on the skin surface both anterior and posterior to the lateral border of the sterno-cleido-mastoid muscle can be seen secondary cancer nodules. The axillary enlargement is not visible.

Schneller (*Archiv für Klin. Chir.*, vol. cxix, p. 169) says that the average age of women afflicted with breast cancer is, according to Winiwater forty-five and three-tenths years, according to Guleke forty-nine and two-tenths years, whereas Yamamoto found the average age of men thus afflicted was fifty-four years, and that the occurrence found in his collection of German statistics was 11,654 female and 167 male cancers.

Relative Occurrence—Statistics.—The occurrence of cancer in the male

breast is about the same in all statistical résumés, namely from 1 to 2 per cent. of all breast tumors. Marmaduke Sheild (*Diseases of the Breast*, 1898, p. 286) found nine cases in males in 628 of carcinoma of the breast. Mülleder (*Arch. für Klin. Chir.*, vol. cxx, p. 686, 1922) found in twenty-one years in von Eiselberg's clinic that there were 600 cases of carcinoma of female breast and twelve in male breast, all patients being over forty years, except one who was twenty-eight. The influence of trauma seems high. Williams found in 2422 primary neoplasms of the breast twenty-five were in males, of which there were sixteen carcinomata, two sarcomata and six benign tumors. Fessler (*Deut. Zt. f. Chir.*, vol. clxxii, pp. 429–37, 1922) found 700 cases of male breast carcinoma in the literature up to 1919. He thinks most cases arise after 57 years of age.

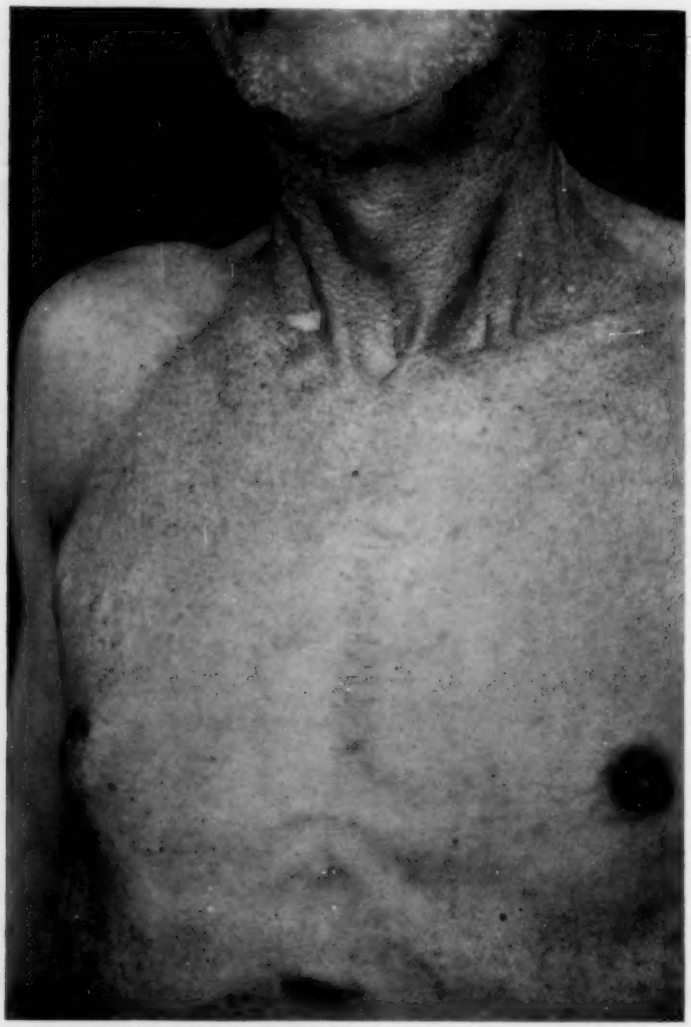

FIG. 3.—The size and extent of the tumor mass of this breast carcinoma can be seen around the right nipple. The secondary tumors in the skin above the breast are evident.

Breast Occurrence.—The right breast seems to be involved with slightly greater frequency. Cumston (*Internat. Clinics*, 1920, vol. ii, p. 25) reviewed a total of 266 male carcinomata and found that the right breast was involved in thirteen instances more than the left. Other collections and reviews of the subject are given by Finsterer (*Deut. Ztschr. f. Chir.*, vol. lxxxiv, p. 202, 1906) Schuchardt (*Arch. f. Klin. Chir.*, vol. xxxi, p. 249) and Schneller (*Arch. f. Klin. Chir.*, vol. cxix, p. 169).

Pathology.—Sarcoma.—Sarcoma is a frequently found malignant tumor of the male breast. It tends to penetrate the underlying fascia and muscle and to ulcerate through the skin early. The tumor does not grow to great size before metastases lead to a termination.

Carcinoma.—Carcinoma is the slowest growing of the malignant neoplasms, usually a small indolent tumor, painless and often unnoticed at the start. It is quite indefinite in its outline, seeming to merge with the tissues about the nipple and breast proper when it is superficial. It invades these structures by extension. Deeper lying cancer early has a hard kernel-like feel—at first freely movable like a small nut, but later fixed, extending into the small amount of breast tissue. In about half the cases the nipple becomes involved. The nipple may be destroyed or may discharge bloody serum. The discharge is only rarely milky. The skin early becomes infiltrated and ulcerates. Retraction of the nipple is not often seen, probably on account of the small size of the male breast and the lack of the connective-tissue bands in the suspensory ligaments. The tumor metastasizes into the skin, muscle, fascia and axillary or other lymph-nodes.

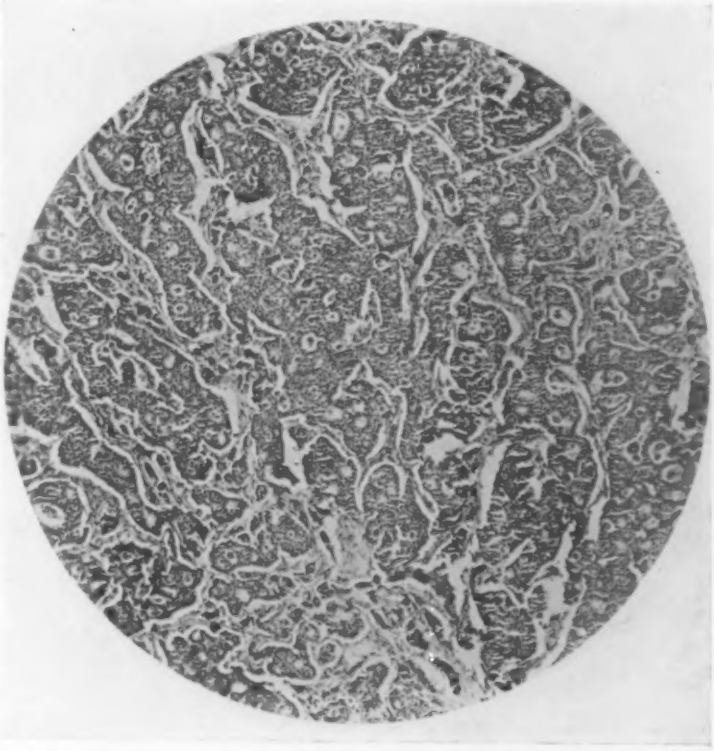

FIG. 4.—The section taken from the main cancer mass of patient No. 2. This is plainly malignant.

Melanoma.—Melanotic male breast cancers occur. I find eighteen cases recorded in the literature (Forgue and Chauvin, *Rev. de Chir.*, vol. lvii, p. 1, January, February, 1919). One existed in a boy aged ten years and all presented rapidly fatal metastases after seeming frequently to take origin in warts or nævi.

Other Tumors.—Angioma, lipoma and chronic mastitis are recorded in the literature, but sarcoma and carcinoma are by far the leaders numerically

in the recorded tumors. Galactocele, one instance of which I record here—seems to be rare. I find no mention of it, although cystic adenoma, to which it may be compared, is known. A large subpectoral lipoma of the mammary region in a man seventy-three years old was reported by Torraca (*La Riforma Medica*, vol. xxxviii, p. 1157, Dec. 4, 1922).

Direct Extension of Cancer.—The thinness of the pectoral fascia in the male demonstrated by Heidenhain (ANNALS OF SURGERY, 1889, vol. x, p. 383) accounts for the close attachment of the breast tissue to the covering of the pectoral muscle. A malignant tumor easily breaks through this fascia and invades the muscle *via* the lymphatics which run from the breast to and along the fascia. A breast cancer may consequently appear to be freely movable on the underlying muscle and yet be invading it along these microscopic lymphatics. Superficial removal cannot be expected to give radical cure. This particular point is referred to emphatically by Speese (*Penn. Atlantic M. J.*, vol. xix, p. 488). Cancerous emboli may also be found in the connective-tissue strands radiating from the primary tumor into the surrounding breast tissue and fascia. Stiles (*Trans. Med. Chir. Soc. Edin.*, 1891, vol. xi, p. 37). Muscle use and contraction after its invasion by cancer must lead to rapid dissemination *via* the lymphatics and by direct extension. The muscle bundles are invaded and destroyed, yet the process may be entirely microscopic. (See Fig. 6.) A study of the degree and frequency of muscle involvement was made by Speese in 100 carcinomatous breasts removed with the muscle attached. Twenty-five specimens presented muscle involvement

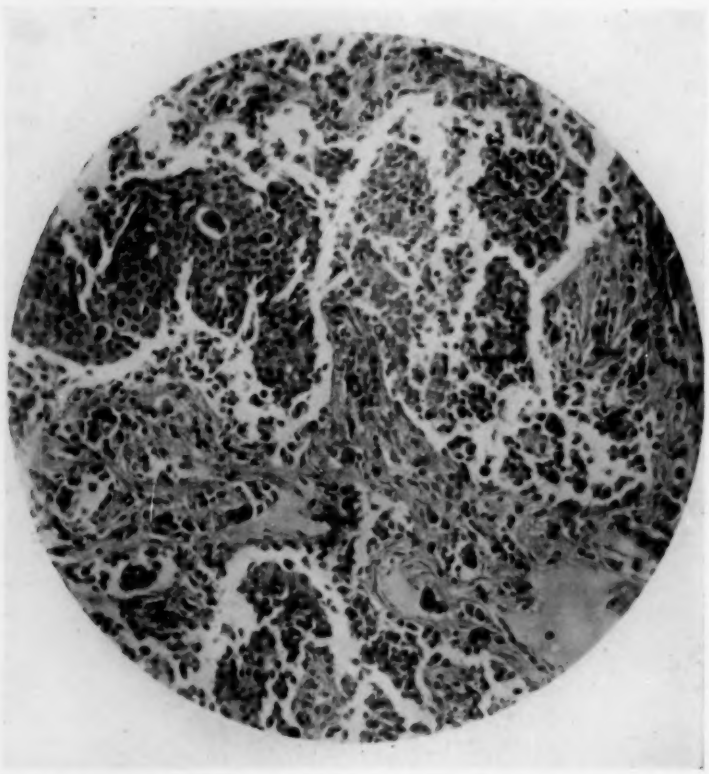

FIG. 5.—A higher magnification of the breast cancer shown in Fig. 4. The invasion of the cancer cells and a few remnants of alveolar structures are discernible.

showing (a) carcinoma cells in contact with muscle on the fascial surface, (b) carcinoma in the lymphatics or spaces between the muscle bundles, (c) muscle tissue destroyed and replaced by carcinomatous invasion. In thirty-five out of the 100 specimens the pectoral fascia was invaded by the cancer and in five where the tumor was not in contact with the fascia there were found nevertheless metastases in the muscle from 1 to 4 cm. distant from the fascial surface. In the male these extensions to muscle must be very frequent on account of the small amount of breast tissue and its immediate proximity to the pectoral fascia.

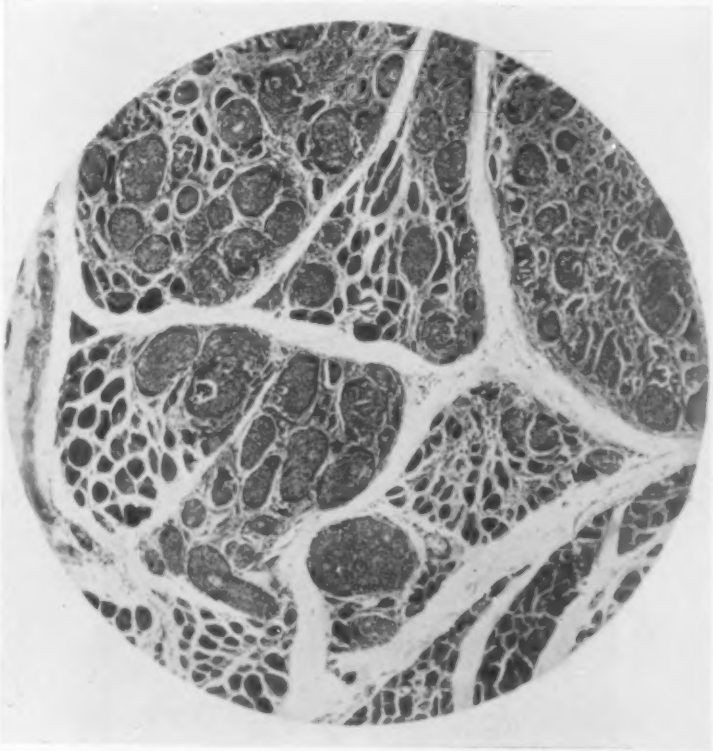

FIG. 6.—A section taken from a cancerous nodule in the pectoralis major muscle of patient No. 2. The septa between muscle bundles, the cancerous invasion of groups of bundles and the process of displacement of individual bundles can be seen. This is muscle metastasis in cancer of the male breast.

Metastases.—The metastases to the skin and to the muscles are especially noteworthy. Multiple small lobules may be found stretching out in a line from the nipple toward the axilla in the skin. The muscle metastases in the early stages are not apparent, they may be microscopic for a long time. Later they lead to pain on exertion and fixation of the tissues on the front of the thorax.

Skin metastases are seen in women but are considered as unusual. Newcomb (*Lancet*, vol. i, p. 1056, May 24, 1924) reported a hard tumor of the left breast in a woman on whose skin there were multiple dark nodules 0.3 to 4 cm. in diameter. These were found scattered over the whole chest, raised above the skin level and near the right breast were several wart-like pigmented tumors. A diagnosis of melanotic sarcoma was made. The postmortem examination showed that the color of the nodules was caused by blood not pigment. There was a papillomatous overgrowth of squamous

skin epithelium lying on a core of secondary carcinoma columns projecting up through the dermis. In some areas carcinoma cysts were present and the cross-cut section revealed that the carcinoma had grown up along the lymphatics to the surface of the skin and then had mushroomed out, forming cavernous blood spaces beneath the surface. Newcomb considered this point remarkable in so far as the squamous epithelium had proliferated over the cancer instead of ulcerating.

Lymph-nodes and Other Metastases.—The axillary lymph-nodes in men appear to be involved late in breast cancer. Statistics show about 60 per cent. invaded at time of operation or autopsy. The detection of their invasion is not difficult as the male axilla is devoid of much fat. The nodes appear discrete and very hard in the average case. In addition to regional metastases we may find a distribution of secondaries in any part of the body—especially the liver, lungs and bones. Of 88 cases recorded by Williams, 5 had bone metastases involving both clavicles, tibia, vertebra and skull.

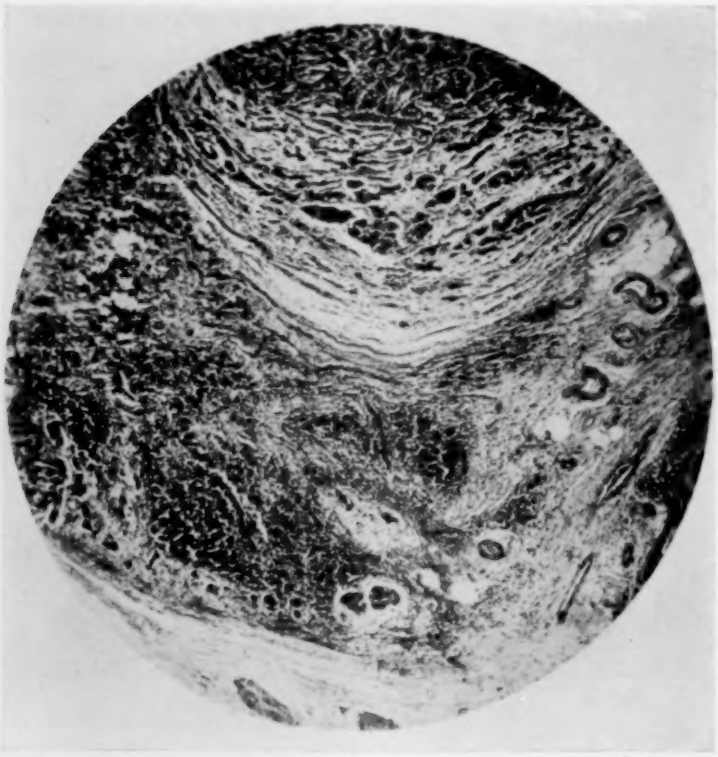

FIG. 7.—A section of an axillary lymph-node removed from patient No. 2. This shows islands of cancerous cells present in the main mass of lymphatic tissue —lymph-node involvement in male breast carcinoma.

Types of Cancer.—Poirier says (*Progres Med.*, Paris, 1883) that the breast in the male is the site of various kinds of cancers. The most common is scirrhus carcinoma, usually of comparatively inactive type. Such tumors show the same features in the male as in the female with the difference that on the whole these are all less marked. The chances of radical cure, varying according to the anatomical features of the tumor, appear to be greater in the male than in the female. The types Poirier described were:

(1) Typical scirrhus, commonest. (2) Pustular and disseminated scir-

rhus. (3) Cancer *en cuirasse* without ulceration. (4) Epithelial carcinoma with metastases in neighboring lymphatics. (5) Encephaloid or medullary carcinoma. (6) Melanotic carcinoma. (7) Cystic carcinoma. (8) Carcinoma with metastases in bone.

Rate of Growth. Ulceration.—On the whole, male breast carcinoma is of slow growth and may commonly exist for as long as three years and sometimes seven to eight years before it really causes symptoms which lead to diagnosis. Skin ulceration appears to come on very late—after four or five years—and the tumor then may take on the aspect of an infected fungoid growth much like the same type in the female. A high percentage of tumors in the male ulcerate, possibly on account of the small amount of breast tissue and its relative superficial position. The rate of growth of the different cell types also is comparable to the analogous form in the female—the melanotic type being extremely malignant and causing early metastases; the adenocarcinoma being quite malignant and the epithelial-celled tumor probably the least malignant of all. The primary tumor in the male breast may be so small or have caused so few symptoms that it is overlooked and the secondary growth attracts attention as a primary tumor.

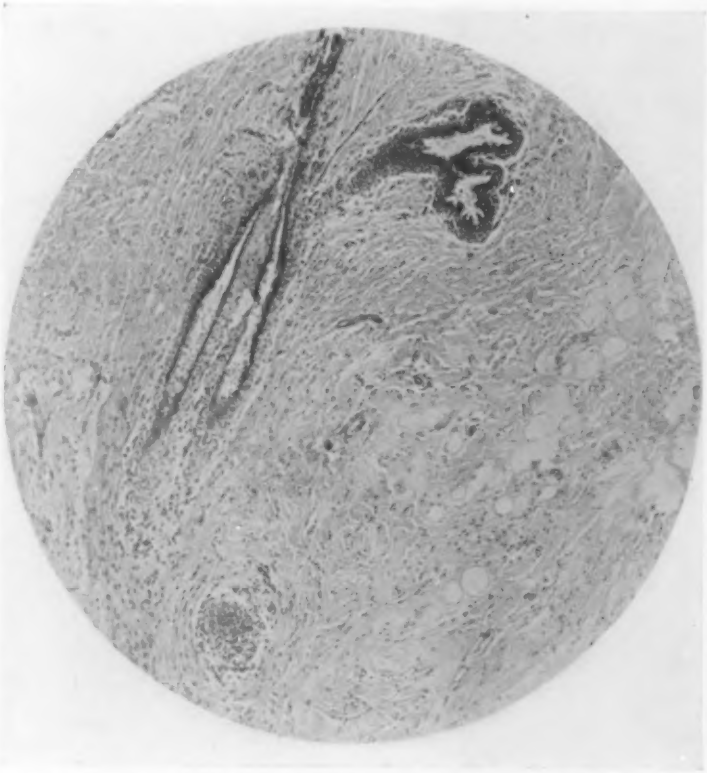

FIG. 8.—Section through the fibro-adenoma of the male breast of patient No. 3. The typical adenomatous male breast of patient No. 3. The adenomatous arrangement with a rich fibrous stroma and the lack of malignant features are noticeable.

Recurrence of Cancer.—Post-operative recurrences are less common in men than women and the tendency to a late recurrence after several years does not seem to exist—most recurrences arising locally soon after operation, possibly because the extent of the minute local metastases in muscle and lymph-nodes is not recognized and a single local excision of the breast tumor is done.

RISCHBIETH (*The Med. Journal of Australia*, vol. ii, p. 205, September 9, 1916) reported an adenocarcinoma with metastatic deposits in a man aged thirty-three years. Two years before he was seen he had noticed a tumor in his left breast. In a year it was removed, but within ten months following recurrence set in. There was no pain, no nipple discharge and a scar an inch long existed over the left nipple. Beneath this was a small hard almond-sized mass and two other small tumors in the breast external to the nipple. The skin was not adherent and all three tumors moved over the deeper tissues. There were half a dozen enlarged hard axillary lymph-nodes. At operation he left behind most of the pectoral muscle and the patient returned in five and one-half months with four small areas of recurrence in the operative scar.

One other case, VERCO'S (*Adelaide Medical Students Society Review*, June, 1916, p. 63) developed evidence of metastases in the cervical spine three weeks after operation for cancer of the male breast. There are too few published reports of radical operation in men on which to base the relative frequency of recurrence after complete surgical removal. LOCKWOOD (*Oxford Medical Publications*, London, 1913, p. 63) recorded an operation in a man fifty-six years of age for breast cancer. He did not perform a complete radical operation as we understand the term to-day, but he did take out the axillary lymph-nodes and the pectoral fascia. Three times in the following year small recurrent nodules in the skin were removed. The patient was alive four years after his operation and free from further growths. Speese gives an average life of fifty-one months after operation on women.

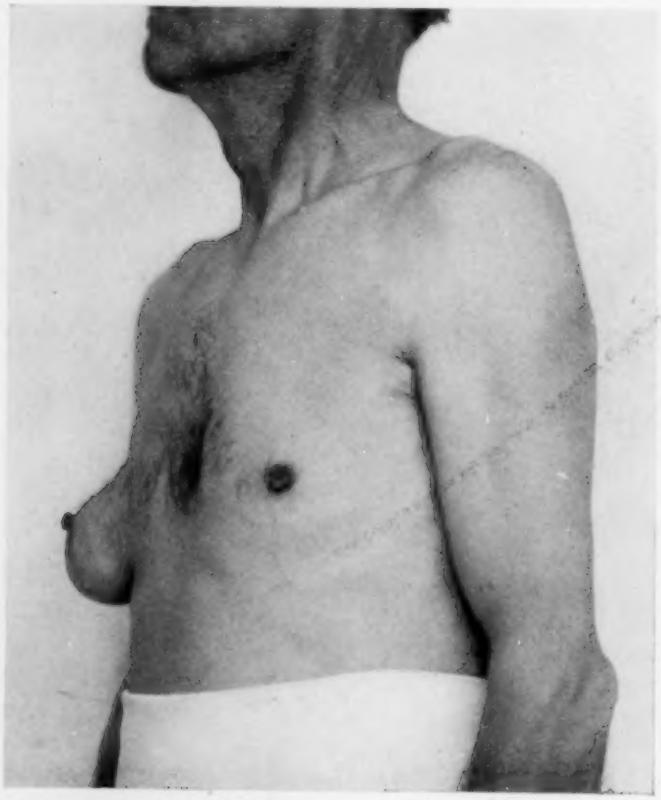

FIG. 9.—Photograph of patient No. 4, showing the tense cystic tumor of the right breast. This was of only three months' duration according to the patient and when removed proved to be a benign galactocele.

Symptoms.—Amongst other common symptoms of breast tumor we may say that pain is frequently entirely lacking. A sizable tumor is often wanting and the constitutional symptoms of weakness, loss of weight and anæmia develop very late. Ulceration may be very early as we have seen, but metastases are long delayed in most forms except the melanotic and round-cell sarcoma.

Treatment.—The treatment of all male breast tumors should naturally rest on the diagnosis. Chronic mastitis and the benign tumors may not require early radical removal, but from our experience with the female breast tumors we can well afford to err on the safe side and do radical removal of the pathologic male breast, innocent as it may seem even to the microscope. Complete removal of pectoral fascia and muscles with block dissection of the axillary, sub- and supra-clavicular lymph-nodes is indicated where there is ulceration or the slightest suspicion of malignancy. When secondary skin nodules are found they and their surrounding skin must be removed.

Operative Difficulties.—In the male radical breast operation frequently will lead to inability to close the wound, because the chest tissues are not so lax, nor is there as much subcutaneous fat as in the female. The skin metastases demanding a great sacrifice of skin will add to this difficulty. Radical removal must be performed in spite of this.

Differential Diagnosis.—Differential diagnosis of the male breast tumors must include a wide range of possibilities such as hydatid cyst, tuberculous abscess of the ribs or breast itself, non-ulcerating gumma, fibroma adenoma, lipoma, mastitis of puberty, galactocele, chronic mastitis, gynecomastia and the various malignant new growths.

SUMMARY

The writer's review of this subject confirms these outstanding points:

(1) The relative occurrence of tumors of the male breast is between 1 and 2 per cent. of all breast tumors.

(2) All different types of tumors—benign and malignant—may be met.

(3) There is usually delayed recognition of cancer of the male breast.

(4) Male breast cancer progresses slowly.

(5) Trauma, especially occupational trauma, seems to be an important etiological factor in male breast carcinoma.

(6) Direct involvement of fascia and muscle by microscopic lymphatic extension is very common in male breast cancer.

(7) A radical operation for removal of malignant breast tumors is just as necessary in the male as in the female and a surgeon should not be fooled by the relative size and non-fixation of the tumor mass—the secondaries are microscopic.

(8) The male offers probably a better prognosis and a longer life expectancy after radical removal of breast cancer than does the female.

PERSONAL CASE REPORTS

The following patients have been operated upon for breast tumors:

CASE I.—Thos. M., white male, fifty-eight years old, single, laborer, entered the hospital, August 13, 1923, complaining of a mass on the left breast which was reddened, not painful, but was enlarging. Four months before he had noticed a "blackhead" at this point which had been squeezed. A red nodule appeared which gradually enlarged. After two months a small amount of purulent material was discharged; since then a slight discharge has continued. The tumor has become dark reddish-purple in color.

His past history furnished no information relative to this tumor and his recent occupation, that of rag sorter, had caused no irritation of his breast. His appearance was that of a healthy, well-developed man. The only abnormal findings were on the left breast, where a fungating irregular dark red pedunculated mass 5 cm. in diameter was found 8 cm. below the midclavicular point. The surface was covered in several areas by a foul-smelling yellow exudate. There was an axillary adenopathy composed of firm rounded and movable pea-sized masses. The blood Wassermann was negative. His blood findings were 90 per cent. hæmoglobin, 11,400 white blood-cells. Blood-pressure 115—88 mm.

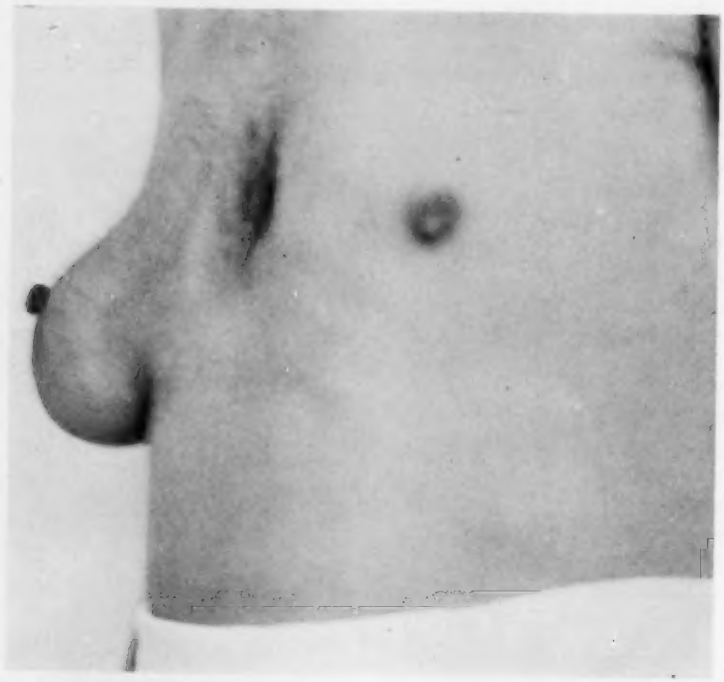

FIG. 10.—A closer view of the galactocle of patient No. 4. The cystic tumor lifted the whole breast, including the nipple,—forward.

On August 20, 1923, a radical breast operation was performed, the excision going wide of the ulcerating area.

Pathology.—The gross specimen was a firm tumor mass located as already described. When the tumor was cut across, the surface was moist and the deeper portions were brown while the superficial portion was whitish. The pea-sized axillary glands were also of the same color and were hard. A frozen section stained with hæmotoxylin and eosin revealed spindle cells in an irregular array.

In paraffin stained section of this block of skin and subcutaneum there was seen a marked invasion of the tissues with spindle cells reaching to and in one place penetrating the covering epidermis. The new growth consisted of closely packed spindle-shaped cells irregularly arranged with acidophile opaque cytoplasm and vesicular hyperchromatic nuclei. The intercellular stroma was not visible. There was wide variation in size, shape and chromatin content of these fusiform cells while mitotic figures were frequent. At the point of ulceration and in the immediate neighborhood were collections of polymorphonuclear leucocytes. (See Fig. 1.) Diagnosis: Fibrosarcoma of the subcutaneous tissues with ulceration of the overlying skin.

The wound healed with some secondary infection. There has been no recurrence to date, twenty months after operation.

CASE II.—Michael C., white male, sixty years old, married, hotel houseman, entered the hospital, September 3, 1924, complaining of a lump in the right breast. This lump was first noticed a month before when he experienced a burning sensation near the nipple and found a tumor just below the nipple with several smaller lumps in the adjacent skin along the upper outer border of the breast. (See Figs. 2 and 3.)

History.—He had lost forty pounds in weight during the last three years and his appetite had been poor. There had been no cough, no bleeding from the nipple, but a doubling in size of the tumor in the last month. His family history contained the information that one daughter had cancer of the breast, one died of tuberculosis, six others were living and well. His general physical examination was of no help as far as any bearing on the present complaint was concerned. The breast tumor was hard, about 3 cm. wide, deep brown, lying just below the right nipple. It seemed to be frozen to the skin and underlying tissues and there were several smaller similar nodules in the skin extending toward the axilla. In the axilla under the edge of the pectoralis major there was a hard mass of lymph-nodes 2 cm. in diameter composed of nodules which were partly round and discrete, partly fused together. The skin nodules were hard, raised above the surface and not umbilicated. No supraclavicular lymph-nodes could be palpated. The nipple was not retracted and the mass of the breast tissues did not appear to be fixed to the chest wall. The left breast was negative. His liver seemed hard and its edge was palpated about three fingers' breadth below the costal margin. No nodules could be felt on its surface. An X-ray of the chest was negative as far as any cancer metastases were concerned. There was a diffuse infiltration of the left apex with a few lines in the right ascending bronchial tree. The hilus markings were as a whole quite prominent.

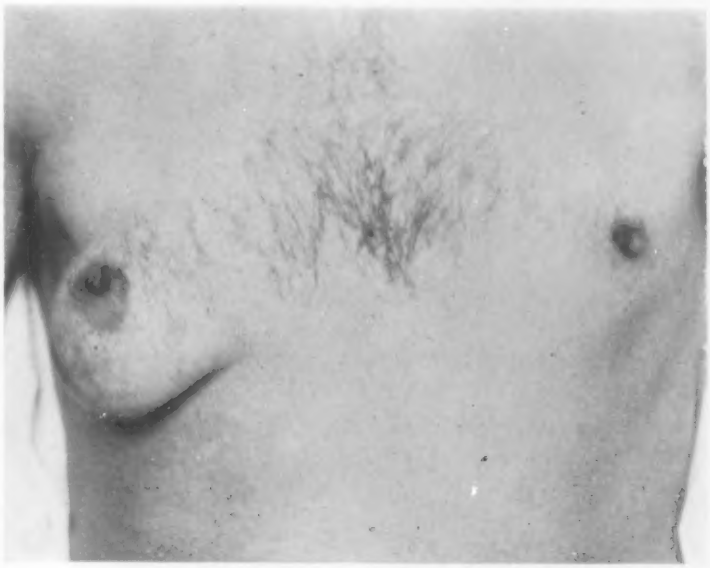

FIG. 11.—Another view of the galactocele of patient No. 4.

Operation.—On September 9, 1924, a radical excision of the breast with both pectoral muscles and axillary contents was performed. On account of the amount of skin which had to be removed some of the healing was by secondary intention. In April, 1925, it is completely healed and there is no evidence of any secondary growth.

Pathology.—The gross specimen consisted of an amputated male breast with the underlying subcutaneous tissues and muscles. There was a firm nodule just beneath the nipple, about the size of a walnut, which was adherent to the skin and surrounding tissues. On cut section it was white with silvery striæ running through it. In addition, within the skin itself there were numbers of hard bean-sized nodules scattered diffusely over the breast, which on section resembled the larger tumor mass. The attached lymph-glands showed infiltration with similar tissue. The pectoralis major muscle contained one tumor nodule about the size of a lima bean. This was definitely within the muscle tissue, invading the bundles.

Diagnosis.—Carcinoma of the breast with metastases to the pectoralis major, axillary lymph-glands and the skin.

Microscopic Description.—In sections taken from this specimen there are seen in the main mass just below the nipple areas of irregular dark-staining epithelial cells

between which a small amount of fibrous stroma is present. The nuclei reveal mitotic figures. A few alveoli are present in the centre of some of these masses. Figs. 4 and 5.) Sections taken from the pectoralis major reveal carcinomatous masses replacing many of the muscle bundles. (Fig. 6.) Tissue from an intracutaneous nodule and from an axillary lymph-gland reveal carcinomatous metastases. (Fig. 7.)

CASE III.—William P., white male, forty-six years old, married, plumber, entered the hospital on the medical service, December 17, 1924, complaining of shortness of breath, swelling of the ankles and scrotum and tumor of the right breast. He was in a state of failing cardiac compensation, the second attack he had experienced. His heart was brought into proper condition by medical treatment with rest, following which he was transferred to the surgical service for operation. His complaint was of a right breast tumor which had existed three months. Its appearance was preceded by dull pain in the breast of about six weeks' duration. This pain was inconstant and the breast had been rubbed with a liniment. No discharge had ever occurred from the nipple. The tumor was above the nipple, hard, size of a hen's egg, slightly irregular and painful to manipulation. The skin over it was not fixed and contained nodulated veins and the tumor was freely movable on the chest tissues. The blood Wassermann was negative. An X-ray of the chest showed only an enlarged heart and pulmonary congestion. The axilla contained no enlarged lymph-nodes, but in the inner triangle of the neck between the sterno-cleido-mastoid muscle and the clavicle there was one enlarged node the size of a pigeon's egg with a smaller one below it. These were also slightly painful.

FIG. 12.—Microscopic section of the galactocele wall. Its dense fibrous structures is seen. On the right hand edge is seen the skin surface. On the left hand edge the secreting layer of cells has been lost. Buried in the fibrous wall are seen the larger dark staining nuclei of compressed secreting elements.

Operation.—On account of the patient's general condition an operation under local anæsthesia with 1 per cent. novocaine and adrenalin solution was thought to be wise. The breast was removed on January 19, 1924, down to the pectoral muscle. Through a separate incision above the clavicle the enlarged nodes there were also taken out.

Pathology.—The description of the gross breast specimen was a moderately soft apricot-sized homogenous tumor mass, outlines well defined, situated around the nipple

area. The nipple and skin over the tumor were freely movable and not puckered. A cut section showed a fatty homogenous mass. The supraclavicular lymph-node was nut-sized and when cut was caseous in its centre. In sections taken from this breast tumor there was seen scattered among the fat and fibrous elements a few epithelial structures. The latter were in places arranged in elongated forms resembling tubules lined by a single layer of columnar epithelium. Elsewhere they appeared to be cut in cross-section. There was a marked increase in fibrous tissue about these glandular elements. (Fig. 8.) Diagnosis: Fibro-adenoma of the breast.

In microscopic sections of the supraclavicular lymph-gland there is seen a central

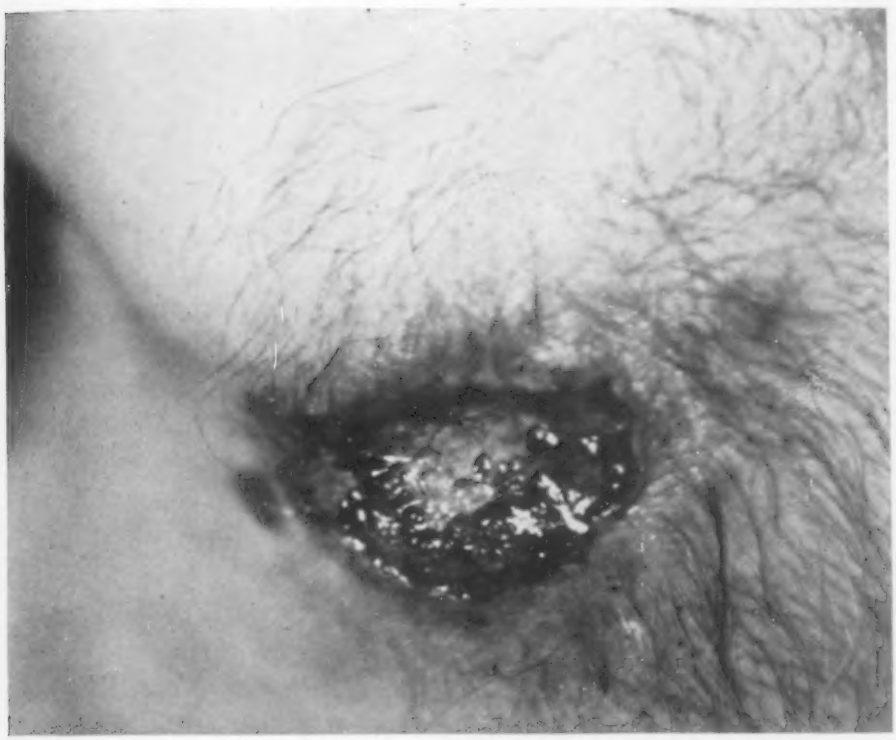

FIG. 13.—Primary ulcerating carcinoma of breast in man aged forty-nine years. This had a duration of about four years; apparently the disease started in or near the nipple, which at this time was completely ulcerated away and the process extended into the pectoral muscle. There were no secondary masses in the skin. There was an axillary adenopathy. On account of the nipple involvement this might be classed as a Paget's disease of the male breast.

caseous mass surrounded by a granulation tissue capsule rich in epithelioid and round cells with an occasional giant cell. There was no evidence anywhere of neoplastic growth. Diagnosis: Chronic tuberculous lymphadenitis.

CASE IV.—William M., while male, fifty-three years old, married, laborer, entered the hospital, January 9, 1925, with the history of a rapidly growing tumor three months old on his right breast; with pain and distention of the right groin and scrotum. He had a right inguinal hernia and hydrocele, which had enlarged rapidly in the last year. His general history was of no interest in regard to the breast tumor. He was a well-nourished white man and our main interest centred on the right breast.

In and around this right nipple there was a rounded mass the size of an orange. (See Figs. 9, 10 and 11.) This was quite uniform, cystic-like and yet firm, not unlike an adolescent female breast. (See photograph.) We feared that he might have a unilateral gynecosmastia, but on repeated questioning he affirmed that the tumor had

been growing only three months since he first noticed it. There were no nodules in the breast and the axilla was normal.

Because of the rapid growth of this tumor we advised radical removal of the breast. This was done a week after admission; both pectorals and axillary contents were removed with the intact tumor attached. The gross specimen consisted of a male breast with the attached pectoral muscles. Below the nipple was a spherical cystic swelling, diameter about 7 cm. The overlying skin was freely movable. On opening into this swelling 145 c.c. of a thin milky fluid with a finely flocculent precipitate escaped. After standing in the ice box twenty-four hours this fluid was found curdled like milk. The wall of the cyst was thin, white and slightly granular. No tumor nodules were noted anywhere in the muscles. Diagnosis: Solitary cyst of the male breast. Galactocele?

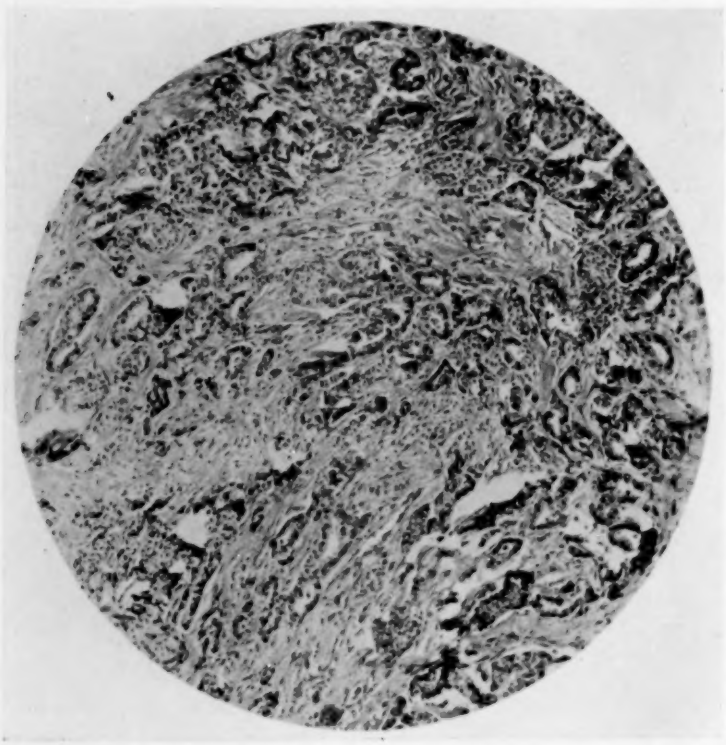

FIG. 14.—Photomicrograph of the primary scirrhous carcinoma of the male breast. The large amount of fibrous tissue is evident in this section taken just beyond the ulcerating edge. There is considerable leucocytic infiltration.

A microscopic section of the cyst wall (see Fig. 12) shows laminated fibrous tissue in closely packed layers. On account of the pressure within the cyst the skin covering was seen to be reduced to almost a straight layer of epithelial cells arranged in typical order from columnar at the base to pavement epithelium on the surface, without any dipping between papillæ. The same pressure may account for the absence of the secreting lining of the cyst, inasmuch as the block for section was not prepared at once and the cells probably disintegrated and were histologically lost.

Scattered through the fibrous tissue of the cyst wall, however, may be found epithelial cells which probably represent the compressed remnants of the original glandular or secreting acini or ducts which caused the milk formation within the cyst.

CASE V.—D. K., Greek tailor, aged forty-nine years, was admitted to the hospital, May 5, 1925. His history was that a pea-sized lump was noticed in the nipple of the right breast in November, 1921. This increased slowly in size until eight months before admission, when in rubbing his skin after a bath the skin over the lump came off. Bleeding and ulceration followed. For the last four months there has been a sero-purulent discharge from the ulcer accompanied by a disagreeable odor. For a year he has been losing strength, been unable to work, and has sustained a loss of 10 pounds in weight.

During this period there have been night sweats and for the last few months, cough followed by a yellow sputum, which was never blood-tinged. There was no cardiac disturbance, except some dyspnœa on exertion. No œdema of the extremities, no abdominal distress or vomiting, and no hematuria, although he had to get up twice each night to urinate. His habits and family history furnished no information in regard to his present condition.

The physical examination showed a well-nourished man, on whose right breast in place of the nipple was an ulcer 4 by 2 cm. in size, extending down into the pectoral muscle, covered with a bloody pus. This ulcer bled very easily when rubbed and its edges were very hard, not undermined. Hard, rod-like extensions beneath the skin and probably beneath or in the pectoral fascia could be palpated extending up to the right axilla. In this axilla were both seen and felt enlarged, hard lymph-nodes, under the edge of the pectoralis major. There were several masses of lymph-nodes, the largest nearly 2 cm. in length. The left breast and axilla were normal.

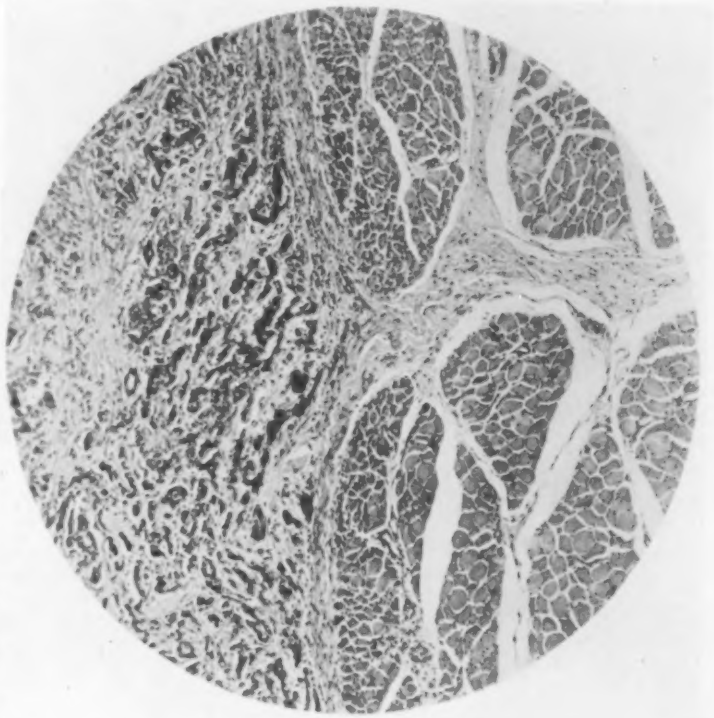

FIG. 15.—Secondary lymphatic invasion in the scirrhous mammary carcinoma of the male. The section was taken from a lymph-node lying beneath the pectoralis major muscles high in the axilla. It was firmly fixed to the muscle and shows leucocytic infiltration probably from infection of the primary cancer ulcer. The scirrhous character is fairly well maintained but the muscle has not yet been invaded.

The regional physical examination made by the interne failed to show any cardiac or chest pathology; abdominal examination failed to permit the palpation of any organ, although the wall was reasonably lax. There was no ascites. An X-ray examination of the chest was ordered, but was never done, although it was reported to me that there was no X-ray evidence of chest pathology which would indicate metastases. The Wassermann blood reaction was negative.

A radical removal of the breast, pectoral muscles and axillary contents was performed May 8, 1925. It was found impossible completely to close the skin after wide excision of the ulcerated area. The patient rallied at first after the operation, but rapidly became weaker with a cough and profuse sputum developing. Death occurred May 16, 1925.

The pathological report of the breast carcinoma specimens removed was: This specimen consists of an amputated breast with the underlying pectoral muscles and the axil-

lary lymph-glands. The skin is elliptical in shape and measures 9 by 15 cm. In the centre is an oval lesion 3 by 5 cm. The border is 1½ cm. wide and deep red in color. The whole area is crateriform in shape, sloping gradually to the centre, which is yellow and 7 mm. below the edges. The surfaces of this cavity are finely nodular, but glistening and clear, and there is no evidence of necrosis. The edge of the lesion is ragged and there is a sharp demarcation between the ulcer and the skin. There are a few long black hairs projecting from one edge. This whole area is hard and fixed to the underlying tissues. The firmness extends from 1 to 2 cm. out from the edge of the ulcer. On either side, 2 cm. from the border of the ulcer, are two discrete nodules 1 cm. in diameter. In the centre of each of these is a shallow ulcerated area similar to that in the primary mass described. There is some fatty tissue about ½ cm. in thickness below all the skin. The primary tumor infiltration extends down through this fatty tissue and into the pectoral muscles below it. In the fascia and loose tissues between the pectoralis minor and major are hard discrete nodules up to 4 mm. in length. There is an attached clump of axillary glands also infiltrated by firm tumor tissue, the largest of these measuring 3 by 2 cm. There is no evidence of a nipple, its site being replaced by the large ulcerated lesion. Diagnosis: Primary ulcerating scirrhous carcinoma of the breast.

The anatomical diagnosis from the autopsy was: Recent, sutured, right radical mammectomy wound; metastatic diffuse carcinomatosis of both lungs; metastatic carcinoma of the right axillary and tracheobronchial lymph-glands; tumor metastases in the liver and pleura; unresolved pneumonia of the left lower lobe; left fibrino-purulent pleuritis; moderate generalized anemia; moderate cloudy swelling of the parenchymatous organs; atheromatous degeneration of the aorta; multiple strictures of the bulbus and penile urethra; pyorrhœa alveolaris; cholelithiasis.

Both lungs showed large areas of metastases which would easily have been apparent on X-ray examination. There was carcinomatous involvement of the pleura and liver, not extensive; the pneumonia was recent (post-operation). This patient should not have been operated upon in the face of metastases. These should be sought by all clinical means at our disposal before a radical breast amputation is performed, although we may believe that generalized and regional metastases in the male follow much later than they do in the female. The size of the lymphatic enlargement in the axilla should be some indication of the possibility of metastases elsewhere if we believe that the blockage there leads to an effort on the part of the carcinoma to spread *via* more difficult paths.

BILATERAL MAMMARY CANCER OPERATIONS*

ULTIMATE RESULTS IN NINETY-EIGHT CASES

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In critically considering the ultimate results following bilateral operations for consecutive bilateral breast cancers, it should be recognized at the outset that there are two distinct classes of patients, first, those in whom the second breast tumor is manifestly a metastasis from the first mammary cancer, evidenced by nodular fascial permeations across the chest, or secondary to node involvement of the second breast. These are simply recurrences after single breast operations, with a very bad prognosis after the second mammary amputation, as is the prognosis with most recurrences, despite all varieties of treatment. The second class comprises those patients whose second breast lesion has no visible connection with the first, having arisen apparently *de novo*, that is, there are no other apparent growths evidenced anywhere else. These are the patients in whom both breast growths *may* be primary, and the prognosis of which we wish to determine.

Unfortunately, in these reported results of bilateral operations, such a perfect division of patients was impossible to make completely because of the frequent deficiency in the reported details of the lesions. Wherever, however, it was indicated that the second breast tumor was accompanied by skin recurrences, such a patient was excluded from the series.

In the replies to the questionnaire sent out by means of which this report was made up, there were not sufficient details given to state the number of patients who had axillary node involvements, or not. It is the author's intention to still further pursue the inquiry as to the influence of node involvement upon the prognosis, and also to ascertain the pathological similarity, or dissimilarity, between the two tumors in the two breasts. It is hoped that those who have volunteered patients included in this report will have the goodness to send to the author details on these points, that a complete report may be made to this Association at a later date. The author desires to acknowledge the great kindness of those who have given to him the patients which have made this report possible.

In this report there are 98 patients with bilateral mammary cancers, 11 of which were simultaneous, while 87 were consecutive. The frequency (Table I) of bilateral breast cancers (including both simultaneous and consecutive together) is 4.9 per cent. of all mammary cancers (in 3132 breast cancers, the bilateral lesions occurred 154 times). Simultaneous bilateral

* Read before the American Surgical Association, May 5, 1925.

cancers occur about once in 500 breast cancers, or .2 per cent. and consecutive bilateral cancers 4.7 per cent. As a means of comparison, the writer has collected the results (Table II) of 1720 operations for unilateral breast cancers; of these, 31.6 per cent. were alive five years after the single operation, while of the 87 patients (Table V) with consecutive bilateral cancer operations, 47 patients, or 54 per cent., were alive five years after the first operation, and 21 patients, or 24.1 per cent., five years after the second operation, which is truly an astonishing finding.

The data as to the ultimate outcomes following operations on these 98 patients for bilateral mammary cancers (Table V) seem to establish:

Firstly, that, compared with the ultimate results following operations for *unilateral* mammary cancer, the extreme pessimism current, regarding the final results following operations for the *bilateral* lesions is not justified.

Secondly, that the second breast cancer, in probably a large number of patients, is a primary growth, entirely independent of the first breast cancer. The following facts speak for the truth of this hypothesis: (*a*) Absence of growths (metastases) elsewhere at the time of the second operation in most of the patients.

(*b*) Histological dissimilarity frequently of the types of the two breast cancers.

(*c*) Impossibility of simultaneous bilateral mammary cancers having any direct etiological connection between them.

(*d*) Hopelessness of the prognosis, if we regard the second breast tumor as a metastasis from the first, since recurrences, after unilateral mammary cancer operations, have a very bad prognosis. These statistics of bilateral operative results do not bear this bad prognosis out, which strengthens the argument for the primary origin of the second breast tumor.

Theoretically, we may argue that presumably the breasts of normal individuals are structurally alike, at least in the beginning. Most authorities, among them Doctor Carrel, have given up the idea of the microbic origin of cancer, this theory being superseded by the supposition that its etiology may possibly be due to local irritation plus some constitutional physico-chemical, or electrical change, which influences the erratic behavior of cells. This change may act on the two breasts differently, one being unaffected, or causing a simple mastitis, while in the other breast, cancer may develop. This unilateral effect is the usual result (95.1 per cent. of all mammary cancers). In other instances, rare to be sure, simultaneous cancers may be set up in each breast (.2 per cent.), the poison acting equally at the same time on the two breasts, or the poison may act unequally in time, each breast consecutively becoming cancerous at different times (4.7 per cent. of all mammary cancers). Speaking almost decisively for each of the bilateral growths being primary is the fact that many of these cancers are dissimilar histologically; thus, Wiener's patient (Table VIII, No. 62) who had adeno-cancer

in one breast and scirrhus in the other, with an interval of 11 years between the two operations, the patient now being well, 25 years after the first operation. Likewise, Primrose's patient (Table VII, No. 10) with simultaneous cancers, one medullary, the other scirrhus; Hitzrot's simultaneous patient (No. 7) had adeno-cancer in each breast. Greenough's consecutive patient (Table VIII, No. 69) had adeno-scirrhus cancer in one breast and medullary in the other. McWilliams' patient (No. 38) was an instance of a consecutive breast tumor with a six years' interval between the two operations, the tumor in each breast being similar histologically; on neither side was there any node involvement. This patient is alive to-day, 15 years after the first operation and 9 years after the second. In the second breast, there was a distinct mastitis, in which the cancer had developed.

Two influences seem likely to be necessary to cause cancer. First, a local irritation, more or less continuous, probably extending over a long period of time; but this, in itself, alone is not sufficient to cause cancer; for example, witness the fact that all pipe smokers do not acquire cancers of the lip, or tongue, only a few do. To the local irritant must be added some general constitutional influence, possibly some physico-chemical or electrical change. In the above patient of McWilliams, the local irritant produced at first a single chronic mastitis. In the majority of women, this chronic mastitis would not go on to form cancer, lacking the constitutional cause; but in this patient, to the effects of the local irritant, was added the essential, unknown, constitutional cause, and we had two consecutive primary breast cancers develop, superimposed upon double chronic mastitis, coming on probably at different times; for, in the opinion of the author, it is impossible to escape the positive conclusion that in this patient, each breast cancer was a primary growth, neither having gone on to axillary involvements, nor to lymphatic skin permeation recurrences. Possibly in the future, little advance over our present methods will be accomplished in treating cancer *after* it has once developed. Efforts will have to be made to determine the general constitutional cause, elimination of which will prevent the inception of the cancer. This will require deep study of the life history of cells and the causes which influence them to develop rightly or wrongly.

Possibly an analogy may be drawn between the paired ovaries and the paired breasts. It is the writer's impression that if one ovary is found cancerous, the second will either be found cancerous at the same time, or subsequently will probably develop cancer. The only access from one ovary to the other is across the peritoneum, lacking direct lymphatic connections, so there may be some constitutional chemical cause added to local irritation, producing independently like lesions in the two organs at the same time or at different times.

Handley states that in a late stage of breast cancer, owing to extension of permeation across the middle line, enlargement of the opposite axillary

nodes often occurs. A little later, deposits of growth are noted in the opposite breast.

We therefore assume that each one of the bilateral cancers is primary when there are no fascial or skin nodules present across the chest, or no axillary lymph-node involvement on the side opposite to the original breast cancer, and when the cancers in the two breasts are of a different histological type. Contrariwise, it is not obligatory to infer that because the two cancers are of the *same* histological type that the second is necessarily a metastasis from the first, since it would be more reasonable to assume that a general cause, acting equally on like tissues, would produce like lesions with no necessary direct anatomical connection between the two.

TABLE I

Results in Single Breast Amputations After Five Years

Judd	150 heard from	30.0 per cent. alive after 5 years
Porter	22 heard from	27.7 per cent. alive after 5 years
Mills	118 heard from	39.8 per cent. alive after 5 years
Sistrunk	218 heard from	36.7 per cent. alive after 5 years
Bunts	695 heard from	16.9 per cent. alive after 5 years
Peck and White	69 heard from	39.0 per cent. alive after 5 years
Greenough and Simmons	69 heard from	32.0 per cent. alive after 5 years
Primrose	76 heard from	44.4 per cent. alive after 5 years
Deaver	150 heard from	26.0 per cent. alive after 5 years
"Total"	1720 heard from	31.6 per cent. alive after 5 years

These figures (31.6 per cent. alive of unilateral lesions, after 5 years) are the results of unilateral operations on all cases, late as well as early. A very favorable prognosis is found in node-free patients, in the unilateral mammary cancers. Thus, G. P. Mills, among cases operated by a number of British surgeons, found a 6-year cure in 62.9 per cent. of node-free patients, while Sistrunk found 64 per cent. alive or node-free patients, 5 to 8 years after the unilateral operations. The prognosis depends, then, upon the presence or absence of node involvement, since the operation itself has become standardized, and can scarcely be extended; as Bloodgood says: "If the lump felt by the patient proves to be cancer, its duration is the only controllable factor in the ultimate cure, and the percentage of recurrences after 5 years gradually rises with each two-month period of time between the origin of the growth and the operation." Rodman (*Atlantic Med. Jour.*, Oct., 1923) says:

1. If a diagnosis is made in the precancerous stage and operation at once performed, 100 per cent. of cures will result.

2. If in the stage of microscopic cancer, 72 per cent. of cures will result after radical operation.

3. If the diagnosis before operation can be practically certainly made, not over 30 per cent. will be cured.

TABLE II

Frequency of Occurrence of Bilateral Mammary Cancers

Bunts	Found in	721 patients,	70 bilateral, or 9.6 per cent.
Davis	Found in	166 patients,	8 bilateral, or 4.8 per cent.
Kilgore	Found in	1100 patients,	37 bilateral, or 3.3 per cent.
Primrose	Found in	125 patients,	11 bilateral, or 8.8 per cent.
VanderVeer	Found in	269 patients,	8 bilateral, or 2.9 per cent.
Dowd	Found in	202 patients,	1 bilateral, or 0.4 per cent.
Payne	Found in	190 patients,	3 bilateral, or 1.5 per cent.
Lockwood	Found in	166 patients,	8 bilateral, or 4.8 per cent.
Braun	Found in	193 patients,	8 bilateral, or 4.1 per cent.
Total	In	3132 patients,	154 bilateral, or 4.9 per cent.

Judd states that the opposite breast is involved in from 10 to 12 per cent. of the late cases.

We may say then that 5 per cent. of patients with cancer in one breast, in the operable stage, will develop cancer in the opposite breast.

Kilgore reports that a patient who has had one breast amputated for cancer is, if she survives 5 years, from three to four times more likely to develop cancer in the second breast than a normal woman of the same age, in either of her two breasts; also that the majority of cancers in second breasts, arising three to four years after the first operation, behave clinically at least like primary new growths—not like a metastasis from the cancer in the first breast.

TABLE III

Simultaneous Mammary Cancers

Bloodgood states that simultaneous cancerous tumors occur in the two breasts about once in 500 patients, or .2 per cent. In the present series of 98 bilateral mammary cancers, simultaneous cancers occurred in the two breasts eleven times, or 11.2 per cent. of the bilateral cases. The results of these eleven simultaneous bilateral operations are as follows:

Living at time of last report		Dead
1 and ½ years		In 4 months
3 years		In 8 months
3 and ½ years		In 1 year
4 years		In 2 years
22 years		In 2 years and 3 months
		In 4 years
5	Totals	6

Thus, only 1 of 11 patients with simultaneous bilateral mammary cancers, or .9 per cent., is alive longer than 4 years after the double operations. It is therefore evident that the ultimate prognosis after operations for two simultaneous breast cancers is much more grave than after operations for two consecutively appearing breast cancers (see Table V). The average duration of life of the 6 dead was 1.7 years.

TABLE IV

Lengths of Time Between Operations upon 87 Consecutive, Bilateral, Mammary Cancer Patients.†

Living (33)			Dead (54)	
2		Six months between operations	8	
5		From 6 to 12 months between op.	13	
7, or	8.3 per cent.	2nd operation within 1 year of 1st op.....	21, or	24.1 per cent.
13, or	14.9 per cent.	2nd operation within 2 years of 1st op.....	29, or	33.3 per cent.
19, or	21.8 per cent.	2nd operation within 3 years of 1st op.....	37, or	42.6 per cent.
21, or	24.1 per cent.	2nd operation within 4 years of 1st op.....	42, or	48.2 per cent.
23, or	26.4 per cent.	2nd operation within 5 years of 1st op.....	46, or	52.8 per cent.
27, or	31.0 per cent.	2nd operation within 6 years of 1st op.....	48, or	55.1 per cent.
0		Between 6 and 7 years	1	
2		Between 7 and 8 years	1	
1		Between 8 and 9 years	1	
1		Between 9 and 10 years	1	
1		Between 10 and 11 years	1	
1		Between 12 and 13 years	1	
33			54	

Totals of Living and Dead Together

2nd operation within 1 year of 1st operation, 28, or 32.1 per cent.
2nd operation within 2 years of 1st operation, 42, or 48.2 per cent.
2nd operation within 3 years of 1st operation, 56, or 64.3 per cent.
2nd operation within 4 years of 1st operation, 63, or 72.4 per cent.
2nd operation within 5 years of 1st operation, 69, or 79.3 per cent.

In 12 patients (13.8 per cent.) the 2nd operation occurred between 6 and 13 years after the first.

† The percentages are based on the total number of patients (87).

The total statistics (Table IV) have been arbitrarily divided into two classes at the time of the reports, the living and the dead, 33 of the former and 54 of the latter. As has been already shown, simultaneous, bilateral, mammary cancers are much more quickly fatal than consecutive, bilateral cancers. It would be fair to assume, then, that in the consecutive, bilateral cancers, the more quickly the second breast operation approximates the first, the worse the prognosis. This assumption is borne out by the fact that within the first year after the first breast operation (Table IV), the second breast operation was performed three times (21 instances) as often in those who have died as in those who are still alive (7 instances). In succeeding years, the individual numbers in the two classes more nearly approximate each other, the percentages in each year remaining almost constantly about double those of the dead, as of the living, the greatest difference in the figures being mainly due to the difference in the number operated during the first year after the first operation. Totalling the living and the dead, it is found that 32.1 per cent. were operated upon for the second breast cancer within 1 year after the first operation, 48.2 per cent. within 2 years, and 64.3 per

cent. within 3 years, and 79.3 per cent. within 5 years. In 13.8 per cent. the second operation occurred between 6 and 13 years after the first.

TABLE V.

Results In Time Since the Double Operations Upon 87 Consecutive, Bilateral, Mammary Cancer Patients, Including the 54 Known Dead and the 33 Known Alive.

Bilateral Operations.

	After 1st operation	After 2d operation	Sistrunk's statistics of 218 unilateral operations
Lived for 3 years	63 (72.4%)	33 (37.9%)	113 (51.8%)
Lived for 5 years	47 (54%)	21 (24.1%)	85 (39%)
Lived for 8 years	31 (35.6%)	15 (17.2%)	80 (36.7%)
Lived for 10 years	19 (21.8%)	9 (10.3%)	

11 lived between 10 and 15 years after 1st operation in the bilateral lesions.
7 lived between 10 and 15 years after 2nd operation in the bilateral lesions.
5 lived between 15 and 20 years after 1st operation in the bilateral lesions.
2 lived 19 and 20 years respectively after the second operation.
1 lived 22 years and 2 are alive 25 years after the first operation.
None are alive longer than 20 years after the second operation.

In attempting to comment on Table V, the author is at a loss to explain the much more favorable results in the 3- and 5-year periods, following the first operation in the bilateral cases as compared with Sistrunk's similar statistics following single operations alone in the unilateral lesions. For, after the first operation in the bilateral cases, 72 per cent. were alive at the end of 3 years, as compared with Sistrunk's 51 per cent.; and 54 per cent. after 5 years following the first operation in the bilateral cases, as against 39 per cent. in the single lesion. Eight years after the first operation in the bilateral cases, the ultimate results are about the same in the bilateral cases as in the unilateral lesions (36 per cent.). From Table IV, we see that one-third of all bilateral patients will develop the cancer in the second breast during the first year after the first operation, and within two years, one-half will have developed the second breast lesion.

From these statistics (Table V), it is seen that the development of the second breast cancer does not shorten the life expectancy after the 1st breast cancer operation whatsoever, which is further evidence of the primary origin of the second breast cancer. About, roughly, 20 per cent. more are alive 3 and 5 years after the 1st operation in the bilateral cases than after the single operation in the unilateral lesions. But as we follow the patients farther along, we find almost the same proportion alive 8 years after the 1st operation in the bilateral cases as 8 years after the single operation in the unilateral lesion (Sistrunk), namely, about 36 per cent. alive in each. From this it would seem superficially as though the second breast cancer has a tendency to develop more frequently in unilateral breast cancers, which are slow in their course but which usually lead to the inevitable fatal outcome in the majority of patients ultimately, whether single or bilateral.

The results as given in Table VI are as astonishing as those set forth in Table V, and are beyond the author's power to explain. Why only 5.7 per cent. died at the end of the first year, after primary amputation, in the bilateral lesions as compared with Sistrunk's 21.1 per cent. dead at the end of the first year, after operation, in the unilateral lesions, it is impossible for him to say. Only a few more proportionately were dead after the second operation in the bilateral patients than obtained after the unilateral operation (25.2 per cent. in the former and 21.1 per cent. in the latter). And the proportions run with about the same disproportion in favor of the bilateral lesions after the first operation through the third and the fifth years, roughly 20 per cent. Three years after the second operation in the bilateral cases, 50.5 per cent. are dead as against Sistrunk's 42.2 per cent. in the unilateral lesions. Dead at the end of 5 years after the second operation are about the same, proportionately, 55 per cent. in the unilateral as against 57.4 per cent. in the bilateral. And so the surgeon may take heart, as well as the patient, for the development of the second breast cancer will not in any degree shorten the life of the patient after the second breast operation, as compared with the life expectancy after the first operation, provided the second breast cancer is not clearly an evident recurrence, coming from the first breast cancer.

TABLE VI.

*Comparison of the Known Dead (54) in the 87 Consecutive Bilateral Lesions with Sistrunk's Known Dead (120) in the 218 Unilateral Lesions.**

	After first operation	Sistrunk	After second operation
Dead at end of 1st year.....	5 (5.7%)	46 (21.1%)	22 (25.2%)
Dead at end of 3rd year.....	24 (27.5%)	92 (42.2%)	44 (50.5%)
Dead at end of 5th year.....	34 (39%)	120 (55%)	50 (57.4%)

In the bilateral lesions, 48 (50.5%) were dead at the end of the 10th year after the first operation, and 53 (60.9%) after the second operation.

In the bilateral cancers, 6 died between 10 and 15 years after the first operation and one died 14 years after the second operation.

* Percentages are based on the total number of patients and not on the total dead.

AVERAGE DURATION OF LIFE OF THE LIVING AND OF THE DEAD AFTER THE BILATERAL OPERATIONS

In analyzing the consecutive cancers in Table VIII, as to the average lengths of life of the living and of the dead, we find that of the 33 (37.9 per cent.) living, the average length of life between the first operation and the last report is 10.8 years, and between the second operation and the last report, the average duration is 7.2 years. Of the 54 (62.1 per cent.) dead, the average length of life between the first operation and death was 4.9 years, and between the second operation and death was 2.3 years.

Duration of life	After 1st operation	After 2nd operation
Of the dead (54)	4.9 years	2.3 years
Of the living (33)	10.8 years	7.2 years

Of the 11 simultaneous cancers (Table VII), 6 are dead, the average duration of life of these, after the simultaneous operations, was 1.7 years; 5 are living, only one of whom has lived longer than 4 years, excluding the one, who is alive 22 years after the operations, the average duration of life of these 5 being 2 years since the operation.

TABLE VII.

Results of 11 Simultaneous Bilateral Breast Cancer Operations.

No.	Operator	Date of operation	Length of life between operation and death	If living, how long since operation, at last report
1.	Vaughan....	10/1902		22 years.
2.	Royster.....		2 years	
3.	Taylor.....	1/1914	27 months	
4.	Codman....	7/1901	8 months	
5.	Downes.....	6/1920	4 years	
6.	Rea Smith..	4/1923		19 months.
7.	Hitzrot.....	1/1922		3 years, adeno-cancer in each.
8.	Erdman.....	3/12/21		4 years.
9.	Payne.....	1/1911–2/1911		3 and ½ years.
10.	Primrose....	14 months before death, one breast medullary, other scirrhus	14 months	
11.	Heyd.....	12/23/23	4 months	
Average length of life of the dead was 1.7 years				Average length of life of the living, excluding the one patient living 22 years, is 2 years.

PROGNOSIS OF MAMMARY CANCERS

Improvement in the results of treatment for cancers of the breast will follow the same lines of development as that obtained in acute appendicitis, namely, early operation before the development of peritonitis in the latter lesion, and in the former, early operation before the involvement of the axillary nodes. It is a goal we must all strive for. The laity must be impressed in season and out that, because a lump in the breast is painless, this is all the more reason for its extirpation. It should be removed at its inception, and the longer the operation is delayed the more gloomy the prognosis, due to secondary involvement of the nodes and skin. The author believes the results of operations for mammary cancers will gradually improve as the laity become more and more instructed as to the necessity of attending

TABLE VIII.

*Results of Operations for 87 Consecutive Bilateral Mammary Cancers.**

No.	Operator	Date, first operation	Date, second operation	Length between operations	Result	Length between first operation and death	Length between second operation and death	Length since first operation if alive	Length since second operation if alive
1.	Buchanan	1/15/1903	12/9/1903	11 months	Died, 12/12/04	2 years	12 months		
2.	Buchanan	7/1899	8/2/1905	6 years	Well, 8/1924			25 years	19 years.
3.	Buchanan	1/8/1907	1913	6 years	Well, 6/14/17			10 years	4 years.
4.	Buchanan	7/14/1908	7/10/1913	5 years	Well, 6/10/17			9 years	4 years.
5.	Buchanan	1/23/1914	12/4/1915	23 months	Died, 5/10/16	23 months	6 months		
6.	Pilcher	3/13/1891	1896	5 years	Died, 1899	8 years	3½ years		
7.	Pilcher	11/1901	1904	3 years	Died, 1905	4 years	1 year		
8.	Pilcher	8/1905	1908	3 years	Well, 1924			19 years	16 years.
9.	Pilcher	9/1905	4/1908	3 years	Well, 1913			8 years	5 years, no report since 1913.
10.	Pilcher	10/1906	5/1907	7 months	Well, 1917			11 years	10 years, no report since 1917.
11.	Pilcher	3/1907	1913	6 years	Died, 1 year later	7 years	6 years		
12.	Pilcher	12/1907	1908	1 year	Died, 1 year later	2 years	1 year		
13.	Pilcher	7/1911	1922	11 years	Died, 1923	11 years	16 months		
14.	Brinsmade	1909	1910	1 year	Died, 1924	15 years	14 years		
15.	Bloodgood			1 year	Well, 15 years			16 years	15 years.
16.	Balch			3 years	Died, 3½ years	6½ years	3½ years		
17.	Balch			6 months	Died, 1½ years	2 years	1½ years		

18.	Connors	1921	1921	4 months	Well			3 years 4 months	3 years.
19.	Jackson			1 year	Died, 3 years	4 years	3 years		
20.	Hupp			2 years	Well, 20 years later			22 years	20 years.
21.	Hupp			5 years	Died, 3 years later	8 years	3 years		
22.	Dowd	1906	4/1908	2 years	Died, 3 months later	2 years 3 months	3 months		
23.	Wainwright	5/1909	8/1909	4 months	Died, 2 months later	6 months	2 months		
24.	Wainwright	11/1912	4/1913	4 months	Died, 4 months	9 months	4 months		
25.	Wainwright	3/1915	12/1915	9 months	Died, 4/1916	11 months	4 months		
26.	Royster			1 year	Died	3 years	2 years		
27.	Royster			1 year	Died	4 years	3 years		
28.	Davis	6/20/1913	6/1915	2 years	Well			11 years	9 years.
29.	Kanavel			8 months	Died	1 year 8 months	1 year		
30.	Kanavel			3 years	Died	5 years	2 years		
31.	Shipley	1915	1916	6 months	Well			9 years	8½ years.
32.	Shipley	8/1920	7/1923	2 years 6 months	Well			4 years	15 months.
33.	Ashhurst	Recurred in	5 months	5 months	Died	9 months	4 months		
34.	Harris	1902	1910	8 years	Well			10 years	8 years.
35.	Eliot	2/5/09	12/28/10	22 months	Well till '24			15 years	13 years.
36.	Codman	4/1912	3/1918	6 years	Died, 3/02	10 years	4 years		

TABLE VIII—*Continued.*

Results of Operations for 87 Consecutive Bilateral Mammary Cancers.

No.	Operator	Date, first operation	Date, second operation	Length between operations	Result	Length between first operation and death	Length between second operation and death	Length since first operation if alive	Length since second operation if alive
37.	Codman	10/1910	3/1913	18 months	Died, 3/15	4 years 6 months	2 years		
38.	McWilliams	9/1910	4/1916	5 years 8 months	Well, 1925			14 year	9 years.
39.	McWilliams	2/1921	4/1923	2 years 2 months	Died, 10/24	3 years 8 months	1 year 6 months		
40.	Eliot	5/8/16	3/2/17	11 months	Died, 1 year	18 months	6 months		
41.	Eliot	10/30/12	1/14/1916	3 years 4 months	Died	5½ years	18 months		
42.	McGuire	1908	1909	1 year	Died, 1909	2 years	1 year		
43.	McGuire	1909	3/27/17	8 years	Died, 1/1/18	9 years	9 months		
44.	McGuire	7/23/13	11/25/17	4 years 4 months	Died, 5/1920	6 years 10 months	2 years 5 months		
45.	McGuire	10/12/16	9/12/17	11 months	Died, 9/5/18	2 years	1 year		
46.	McGuire	12/31/18	11/5/19	11 months	Alive, recurrence '24	6 years	5 years		
47.	Kellar	1912	1913	6 months	Died, 12/23. "Spinal meta"	11 years	10 years		
48.	Rea Smith	2/1914	2/26/1924	10 years	Still alive			10 years	9 months.
49.	Rea Smith	1915	1/7/22	7 years	Died	8 years 4 months	16 months		
50.	Rea Smith	4/25/22	8/11/22	4 months	Died	1 year	7 months		

51.	Royster	3/1/18	11/1/20	21 months	Living			6 years 8 months	4 years.
52.	Willy Meyer	3/1899	12/1900	1 year 10 months	Well			8 years 1 month	6¼ years.
53.	Willy Meyer	1908	1909	1 year	Well			17 years	16 years.
54.	Willy Meyer	6/29/08	3/28/11	2 years 9 months	Well			8 years 3 months	5½ years.
55.	Willy Meyer	4/19/15	11/5/15	2 years	Died	4 years	2 years		
56.	Willy Meyer	4/9/16	11/1920	4 years 7 months	Died	6 years	16 months		
57.	Hitzrot	1906	10/1908	18 months	Died	3 years	9 months		
58.	Clinton	1916	1917	1 year	Well			9 years	8 years.
59.	Lyle	6/2/19	12/12/20	1 year 6 months	Died, 9/14/24	5 years 3 months	3 years 8 months		
60.	Lyle	11/16/21	12/14/23	2 years	Died, 2/1924	2 years 2 months	1 year 2 months		
61.	Lyle	6/10/08	12/15/09	18 months	Well			6 years	4 years, 6 months.
62.	Wiener	1900 adeno	1911 scirrhus	11 years	Alive			25 years	14 years.
63.	Payne	2/10/07	1/1910	3 years	Died	4½ years	18 months		
64.	Payne	10/1906	11/1911	5 years	Living			18 years	13 years.
65.	Bancroft	3/1918	4/1922	4 years	Well			4 years	2½ years last report.
66.	Bancroft	6/28/12	7/8/21	9 years	Living			12 years	3 years, 3 months.

TABLE VIII—*Continued.*

Results of Operations for 87 Consecutive Bilateral Mammary Cancers.

No.	Operator	Date, first operation	Date, second operation	Length between operations	Result	Length between first operation and death	Length between second operation and death	Length since first operation if alive	Length since second operation if alive
67.	Woolsey.....	1911	4/14/22	11 years	Died	12 years 8 months	20 months		
68.	Greenough.....	8/28/18	11/23	5 years 3 months	Well			7 years 4 months	2 years.
69.	Greenough.....	11/10/20 adeno-scirrhus	6/20/24 medullary	3 years 7 months	Well			4 years	4 months.
70.	Primrose.....			8 months	Died	3 years	2 years 4 months		
71.	Primrose.....			1 year	Died	1 year 10 months	10 months		
72.	Primrose.....			1 year 4 months	Died	2 years 7 months	1 year 3 months		
73.	Primrose.....			1 year 6 months	Died	2 years 2 months	8 months		
74.	Primrose.....			2 years	Died	2 years 5 months	5 months		
75.	Primrose.....			2 years 2 months	Died	2 years 10 months	8 months		
76.	Primrose.....			2 years 8 months	Died	4 years 4 months	1 year 4 months		
77.	Primrose.....			2 years 10 months	Died	8 years	5 years 2 months		

78.	Primrose	11/1910	3/26/23	12 years 4 months	Died	14 years	1 year 6 months		
79.	Peterson	6/3/09	11/10/22	13 years 5 months	Well			15 years 8 months	2 years. 3 months.
80.	Peterson	7/1919	7/1920	1 year	Well			5 years 8 months	4 years. 8 months.
81.	Peterson	4/27/1921	12/18/22	1 year 8 months	Well			4 years	2 years. 4 months.
82.	Brewer	6/30/1914		8 years 3 months	Died	11 years	2 years 9 months		
83.	Darrach	7/1911	12/1911	6 months	Died	10 years	9 years		
84.	Peck	2/14/17	7/10/24	7 years 5 months	Living			8 years	7 months.
85.	PresbyterianHospital	12/16/1914	12/16/1916	2 years	Living			3 years 3 months	1 year. 3 months.
86.	Heyd	8/30/1920	10/1922	2 years	Died	2 years 6 months	4 months		
87.	Heyd	4/1919	9/1922	3 years 4 months	Died	3 years 8 months	4 months		
	Average in years					4.9	2.3	10.8	7.2

The average duration of life of the entire 87 patients is 7.2 years after the first operation and 4.2 years after the second operation.

* Patients in this table who have recurrences at time of report are classed as died at that date. Of those who are alive without recurrences, length of life is calculated up to date of last report.

to tumors of the breasts immediately. To him it is a very encouraging thought that, if we operate on these tumors before axillary node involvement, 65 per cent. will be alive after 5 years. The profession generally must be instructed not to temporize with these patients, with local applications, X-rays, radium or what-not, but to seek immediately the only possible means that give hope of a lasting benefit, namely, wide operative removal of the tumor with the axillary nodes. After surgery has done all that it can, post-operative X-ray treatments should be instituted, these being given not with any expectation of killing any chance cancer cells which may have been left, but with the idea simply of *delaying* their progress and development.

It must not be overlooked that the average age of death in this country is now 58 years. Over 50 per cent. of mammary cancers occur in women over 50; so that if the laity can be sufficiently instructed to have these tumors removed early before node involvement takes place, 65 per cent. of them will be alive from 5 to 8 years after operation, at which time they will have arrived at the age of the general American community.

PRE-OPERATIVE AND POST-OPERATIVE X-RAY TREATMENTS

The author believes that he voices the great disappointment of surgeons in not obtaining more definite good results in treating recurrences after operations for mammary cancers. How frequently it happens that post-operative recurrences appear directly in the region where powerful radiation has been applied, which gradually increase in size despite all degrees of radiation. When a patient with a cancer of the breast comes to the surgeon, it is usually late. In Sistrunk's statistics of 218 unilateral cancers, in 60.5 per cent. the axillary nodes were already involved. With such involvements, only 19 per cent. were alive from 5 to 8 years after the operation, while in those without such involvement, 64 per cent. were alive from 5 to 8 years after the operation. So that the involvement, or non-involvement of the nodes, seems to be the greatest factor in the prognosis following operation. Is it not then foolish to still further delay from two to four weeks in order to give pre-operative X-ray treatments, during which time the axillary nodes *may* become involved, if they are not already affected, and if they are already involved, the delay will only allow further extensions of the process to take place?

That pre-operative X-ray treatments because of the large area to be radiated can appreciably influence favorably both affected axillary nodes and breast tumors without unduly delaying the only possible hope of a cure, namely, operation, stretches one's credulity. The author begs leave to quote an acknowledged authority on the subject of X-ray treatments in mammary cancer, one who is not previously prejudiced for or against such treatments.

Dr. Francis Carter Wood (ANNALS OF SURGERY, February, 1925, p. 559) says: "There is no real scientific or clinical knowledge which permits final judgment on the value of pre-operative radiation. There are many assumptions made by radiologists that have no foundation in fact, one being, for

example, that radiation closes the lymphatics. Clinically, it should be perfectly evident that pre-operative radiation does not close the lymphatics as invasion of skin areas after heavy radiation is not infrequent. Experimental work has also shown that lymphatics in animals cannot be closed by the X-ray, although the terminal arterioles can be. Another objection is that the cancer cells cannot be seriously damaged without equal damage to the surgical field. If 50 per cent. of the cancer cells are killed, 50 per cent. are left in perfect health at a sacrifice of one to two weeks' time. If the tumor shrinks the patient may refuse to be operated on at all. But there is no evidence that sufficient damage is done to the tumor cells to warrant the delay in using pre-operative radiation. If all the cancer cells could be killed, surgery would be unnecessary. From a practical point of view, therefore, the procedure has nothing to recommend it.

"As to post-operative radiation, that is also somewhat in the experimental stage, but on a much firmer footing because one does see superficial recurrences disappear. Only long clinical experience can determine its final value. One thing, however, the surgeon seems to forget in criticizing the failures: the X-ray cannot make cancer grow where cells have not been left.

"In general, it is best to remove the tumor surgically up to the border line of operability and then ray. More skin should be removed than is commonly done, for better results, as regards skin recurrences, are obtained when large areas of skin and fascia are removed. Then all patients should have post-operative radiation for at least two years. It can be done cheaply and effectively without interfering with the patient's work. But there is one very important phase in all post-operative radiation. Once a primary or recurrent tumor has been radiated and has become quiescent, it should not be excised, for rapid and extensive recurrence is apt to follow. Old channels are opened and passage of the tumor cells into the rest of the body is brought about by the surgical procedure."

RÉSUMÉ

1. In 1720 operations for unilateral mammary cancers, 31.6 per cent., were alive 5 years after the first operation, taking all cases as a whole.

2. About 65 per cent. of patients with unilateral mammary cancers with no node involvement will be alive 5 years after the operation.

3. In 3132 patients with breast cancers, bilateral mammary cancers occurred in 5 per cent. (simultaneous .2 per cent., consecutive 4.7 per cent.).

4. Of 11 simultaneous cancers, only one is alive longer than 4 years, indicating a much more grave prognosis following operations for simultaneous cancers than for consecutive bilateral lesions. The average duration of life of those who have died after the two simultantous operations was 1.7 years.

5. The nearer the second operation, in the consecutive bilateral lesions, is to the first, the worse the prognosis. Three times as many of those who are dead were operated upon for the second breast lesion within one year after the first breast cancer operation, as of the living.

6. Of the 87 consecutive, bilateral mammary cancer patients, 72.4 per cent. are alive 3 years after the first operation, and 37.9 per cent. after the second breast operation; alive for 5 years are 54 per cent. after the first operation and 24.1 per cent. after the second operation; while alive 8 years after the first operation are 35.6 per cent., and after the second 17.2 per cent. These figures indicate that the prognosis for living 3 and 5 years after the first operation, in the bilateral lesions, is much better (20 per cent.) than after the operations for an unilateral mammary cancer. The reason therefore is not clear.

7. Patients usually come late to operation with mammary cancers. About 60 per cent. already have axillary node involvement, which involvement decreases the 5-year cures by 30 to 40 per cent. Hence the uselessness of further delaying operation for pre-operative X-ray treatments, since there is no scientific nor clinical evidence that sufficient damage is done to the tumor cells in the breast or lymphatic nodes to warrant delay.

8. In the consecutive, bilateral mammary cancers, the average duration of life, after the first operation of those who have died, was 4.9 years, and after the second operation, 2.3 years; of the living, the average duration of life after the first operation is 10.8 years and after the second operation, 7.2 years.

9. Speaking for the primary origin of many of the second breast cancers are:

(*a*) Absence of metastases elsewhere.

(*b*) Histological dissimilarity of the two tumors.

(*c*) Impossibility of simultaneous mammary cancers having any connection between them.

(*d*) Hopelessness of the prognosis (not borne out by these statistics) if we regard the second breast tumor as a metastasis from the first.

PSEUDO RECURRENCES AFTER RADICAL AMPUTATION OF THE BREAST FOR CARCINOMA

By Alexis V. Moschcowitz, M.D.
of New York, N.Y.

Local recurrences after amputation of the breast are as a rule easily diagnosticable. About five years ago I had an experience which proved to me that not every tumor situated in or near the cicatrix after a radical breast amputation represents a local recurrence. My error in diagnosis in this case made a profound impression upon me, and placed me on my guard, so that when I saw two other cases in subsequent years I was enabled to recognize the correct nature of these tumors, although I had difficulty in convincing some excellent colleagues that these were not true recurrences. I deemed these cases therefore as worthy of being placed on record, for their correct recognition is obviously of the highest importance.

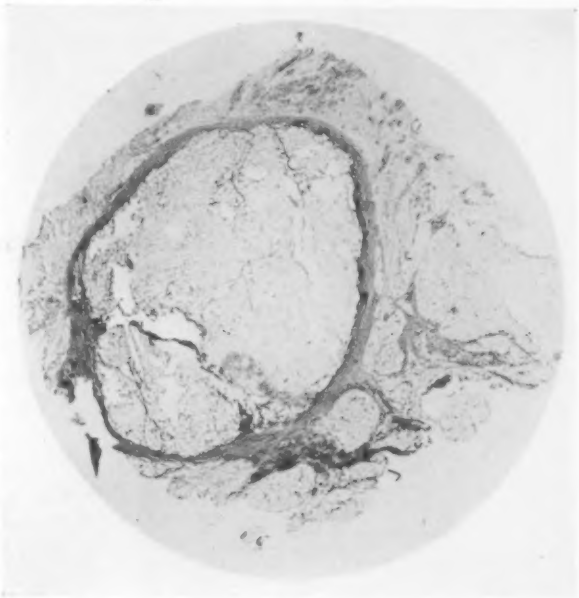

Fig. 1.—Cyst with fibrous wall; cavity is filled with adipose tissue. On the inner side of the wall scattered in various portions are giant cells of the foreign body type.

These "recurrences" are characterized by the appearance within the operative field of tumors which are exceedingly firm and of a bony hardness closely simulating that of scirrhous carcinoma. They vary in size from a pea to a centimetre or more in diameter, and are located either within the skin or subcutaneous fat. They may be adherent to the chest wall itself. In two of my cases the nodules were in or near the axillary portion of the scar; in the third case the nodule was adherent and immovable on the chest wall. The nodules are not tender; the skin overlying may or may not be adherent. They do not apparently increase in size in the course of many weeks' observation. They are circular or slightly elliptical or irregular in shape. Upon excision even gross inspection fails to reveal the characteristic appearance of malignancy. There are apparently two varieties. (1) Small circular masses of compact fibrous tissue. (2) Small circular cysts with a well-developed fibrous wall containing gelatinous-like contents. The microscopic appearance

will be discussed later. I have called these tumors "pseudo recurrences" or foreign body cysts.

CASE REPORTS

CASE I.—Katherine S. consulted me April 7, 1920. Several months ago she noticed a slowly increasing tumor in the right breast. Physical examination revealed a tumor the size of a hazel-nut with extensive glandular involvement. April 14, radical amputation of the breast by the Willy Meyer method. April 28, discharged well. No post-operative radiation.

July 7, 1920, the patient again consulted me and stated that a few days before she noticed a small mass near the middle of the cicatrix. This mass was very firm and hard, neither painful nor tender, and gave all characteristics of a recurrence. July 14, in local anæsthesia, the entire mass was excised down to the ribs through an elliptical incision. The excised specimen showed a small cyst containing a little grumous material, with a very thick, firm capsule. Unfortunately no microscopic examination was made.

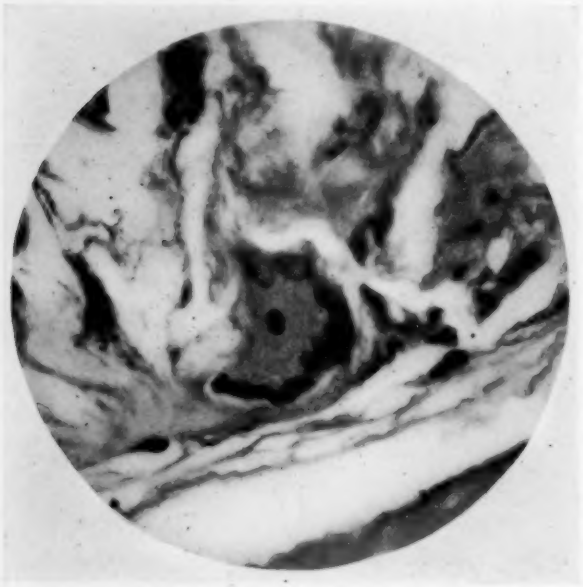

FIG. 2.—Typical giant cell along the fibrous wall of the cyst in Fig. 1.

CASE II.—T. F., fifty years of age, was first seen by me July 4, 1922. Three weeks ago a small lump was noticed in the left breast. In view of the fact that a similar lump disappeared from the right breast on a previous occasion, the present mass was kept under observation for a while. Three days before admission to the hospital an infiltrated gland was palpated in the axilla.

July 5, 1922, typical amputation of the breast. Pathological examination by Doctor Mandlebaum is as follows: "Microscopical examination of the tumor removed from Mrs. F. shows a scirrhous carcinoma arising from duct epithelium. Some of the ducts are filled with a necrotic secretion containing lime salts and cholesterin, therefore the process has existed for a considerable period of time. The axillary lymph-nodes are extremely involved."

Primary union was obtained and the patient was discharged with a completely healed wound in eleven days. She then received post-operative radiation. At this time already there was noted a small nodule adherent to the chest wall approximately in the mid-axilla. Soon thereafter two or three other nodules appeared on the humeral portion of the cicatrix. All of these were regarded as a recurrence by several collagues who saw her, but I suspected otherwise, for I did not recall ever having seen a local recurrence follow so soon after a radical operation.

In October, 1923, I insisted upon the excision of these nodules in order to clarify the feeling of uncertainty in the minds of both the patient and several colleagues who saw her with me. This was accordingly done with local anæsthesia; ideal primary union

resulted, but within three weeks the cicatrices, presumably on account of the preceding radiation, slowly broke down and healing was exceedingly slow.

The excised material was submitted to Doctor Mandlebaum, who rendered the following report:

"The material submitted consists of three narrow strips of skin with subcutaneous fat, with a nodular mass embedded in each, the smallest being 4 mm. in diameter and the largest 8 mm. in diameter. A cross-section through each of these nodules shows a cystic cavity surrounded by a thin wall of connective tissue. Two of the cysts are filled with and surrounded by fat, the third one, however, which is directly below the skin, appears to be empty.

FIG. 3.—Portion of cyst wall containing fat crystals.

"Microscopical examination shows a rather interesting picture. The two larger cysts are limited by a thin wall of long branching strands of fibrous connective tissue, the seat of hyaline degeneration. Attached to the inner wall one notices an occasional giant cell of foreign body type. The cyst is filled with fat, apparently normal in character, but here and there one notes some degeneration and a few fatty acid crystals arranged in a fan-like or feathery form. These crystals, evidently the end result of a chronic inflammatory process or some form of irritation, are more marked in the empty cyst directly beneath the skin than in the larger cysts in the adipose tissue proper.

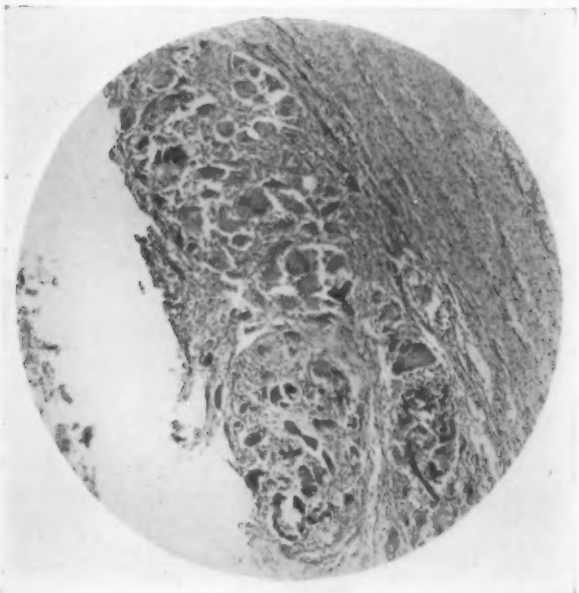

FIG. 4.—Section of wall showing foreign body giant cells. Near the lower angle there is to be seen a black line, a foreign body possibly silk or catgut.

"The process, in all probability, is due to the presence of some foreign body, with a secondary reaction and the formation of a fibrous connective-tissue wall of a protective nature."

CASE III.—Lena V., forty-six years of age, was referred to me by Doctor Abel, in December, 1923, for a small tumor in the left breast

of one year's duration. The corresponding axillary glands were greatly enlarged.

December 18, 1923, radical amputation of the left breast. January 14, 1924, discharged well. The pathological report of the excised specimen by Doctor Mandlebaum reads: "Scirrhous carcinoma of the breast with involvement of the axillary lymph-nodes." Patient received no post-operative X-ray treatment.

November 14, 1924, the patient accidentally noticed a small tumor near the outer margin of the cicatrix of the previous operation, the location of which was approximately in the mid-axilla. I found an exceedingly firm, not tender mass about one centimetre in diameter; a second smaller mass was found in the cicatrix at about its middle. Both tumors gave me the impression of a carcinomatous recurrence.

November 19, 1924, in local anæsthesia excision of a wedge-shaped mass of tissue including the overlying skin and all of the fat surrounding the mass palpated prior to the operation. A similar procedure was carried out on the smaller anterior mass.

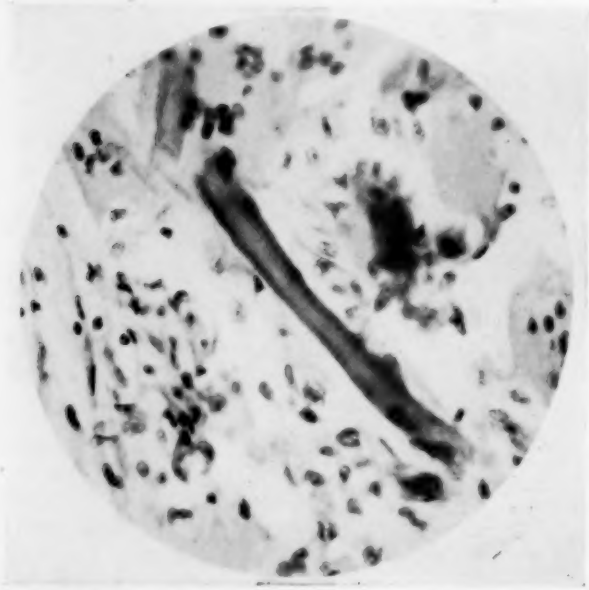

FIG. 5.—High power section of Fig. 4 showing foreign body.

The subsequent very careful examination by Doctor Mandlebaum is as follows:

"The specimen consists of a small, rather firm, nodule surrounded by fat. Microscopical examination of this nodule shows a loosely woven connective-tissue stroma infiltrated with a large number of lymphocytic cells and an occasional polynuclear cell, in other words, a chronic inflammatory process, mild in character. The interesting feature, however, is the presence of several foci of large giant cells of foreign body type. In some of these foci one sees short strands of deeply staining material with parallel borders entirely surrounded by phagocytic giant cells. There is no doubt that the strands are foreign bodies. Whether they are cotton fibres or unabsorbed ligature material one cannot determine with any degree of accuracy, but the lesion is quite characteristic of an irritative inflammatory process due to the presence of a foreign body."

It is very surprising that the condition described is not encountered more frequently. On the other hand, if it is encountered it is astonishing that so little attention has been paid to it, that no one has found it worth while to report it. A fairly comprehensive search of the literature by my adjunct, Doctor Colp, failed to reveal a single instance in relation to carcinoma of the breast; in fact, this search revealed only a single reference which discussed a related occurrence.

GADE (Falsche Geschwulstrecidive, Verursacht durch Einheilung von Aseptischen Fremdkoerpern (Verbandstoffen) Deutsche Medizinische Wochenschrift, 1896, p. 430), reports two cases of which case two is of particular interest. The patient was a young woman, twenty-nine years of age, upon whom a tumor the size of a pea was extirpated from the mucous membrane of the cheek, just at its junction with the superior maxilla.

No microscopic examination was made of the specimen. About one month after the operation this patient again presented herself to her physician with a tumor at the site of the previous one.

The new tumor, somewhat larger than the first one, was also extirpated. On section it was of a peculiar yellowish color and had a homogeneous succulent appearance which, considering the very rapid recurrence, was exceedingly suspicious of a carcinoma. The microscopic appearance, however, spoke absolutely against it; the main mass consisted of young connective tissue with numerous cell masses. On close inspection numerous cotton threads, surrounded by leucocytes and giant cells were to be seen within these cell masses.

In concluding his article Gade states that he assumes that such false recurrences cannot nowadays (1896) be very rare. If the microscopic examination is not made, these recurrences may give rise to a suspicion of malignancy and not infrequently also to needless worry and anxiety.

CONCLUSIONS

(1) Three cases of pseudo recurrences after radical extirpation of the breast for cancer are reported.

(2) These pseudo recurrences simulate physically true recurrences.

(3) They possess the following characteristics:

(*a*) They appear very soon after the operation.

(*b*) They are situated within or very close to the cicatrix.

(*c*) They are painless and hard.

(*d*) They do not increase in size.

(4) Microscopically they represent foreign body cysts. The foreign body being either a catgut ligature or a gauze thread.

ETIOLOGY OF CANCER OF THE STOMACH*

A REVIEW OF ONE HUNDRED SIXTEEN CONSECUTIVE CASES OF CANCER OF THE STOMACH WITH PARTICULAR RELATION TO ETIOLOGY

By Hugh Cabot, M.D.

and

George C. Adie, M.D.

of Ann Arbor, Mich.

The first known reference to carcinoma of the stomach developing on a preëxisting ulcer was made by Cruvielhier in 1839, when he said that a simple ulcer of the stomach in people suffering from "diathise cancereuse" might change into cancer. This was followed three years later by the statement of Rokitansky in which he observes that ulcer appears together with cancer and in that case as a rule it is easy to see that the carcinoma had its origin in ulcer. Dittrich, in 1848, examined 160 cases of gastric carcinoma and only in one case did he find carcinoma in the margin of an ulcer, and even this he regarded as a coincidence. Steiner and Wollman in 1868, Meyer in 1874 and Lebert in 1878, all agreed with Cruvielhier that carcinoma developing on an ulcer only rarely exists. A sudden transition to exactly the opposite view was made in 1882 by Zenker, who proposed the idea that all gastric carcinoma originated in ulcer. During the following year, Hauser, a pupil of Zenker's, published an extensive investigation on the subject. From his morphological description, Hauser maintained that the atypical epithelial changes in ulcer of the stomach were prestages of cancer. However, Friedlander and Cohnheim have shown that the morphology of epithelial proliferation is not limited to the stomach and ulcer, but that, at any place where chronic irritation causes the formation of granulation tissue and where epithelial tissue is present, an epithelial proliferation may appear, which frequently results in an atypical and to a certain degree, cancer-like appearance.

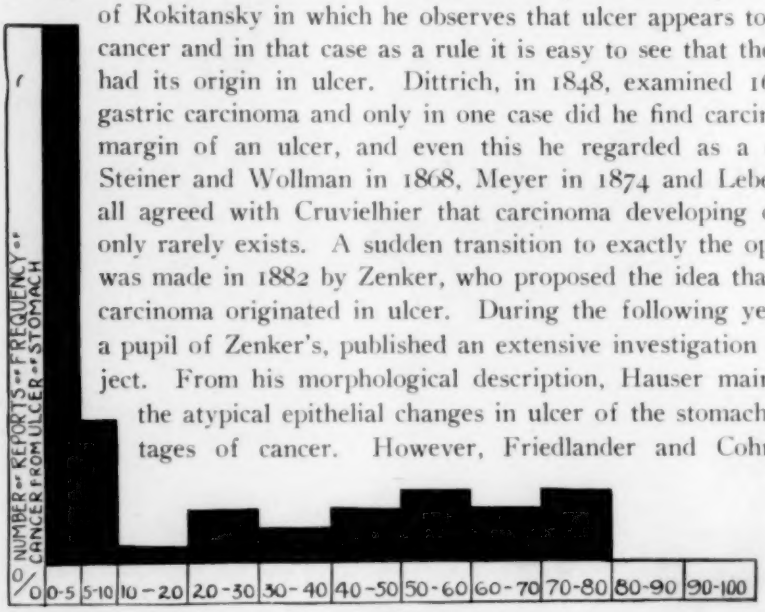

Fig. 1.—1906 to 1915.

Tripier and his pupils, Duplant and Saneroth, in 1900, from morphological and clinical observations, advanced the theory that the ulcero-cancer was not a simple gastric ulcer with carcinomatous degeneration, but a cancer, which in many respects bears a resemblance to the ulcus rodens of the skin. The growth of a gastric carcinoma is so slow and its tendency to ulcerate so

* Read before the American Surgical Association, May 4, 1925.

pronounced, that it is often difficult to find carcinoma cells in the lesion. Tripier did not produce any scientific evidence to support this view, merely stated it as a theory. It was not regarded very highly in France because of the opinions of such men as Bouvert, Dieulafoy, Mathieu, Hayem and Audistere, who all stood for the cancer *ex ulcus* theory.

Without doubt, the theory that has caused the most discussion and led to a great deal of work on the subject, is the one claiming the development of carcinoma in a preëxisting ulcer of the stomach. From a fairly comprehensive review of the literature there are found at least 82 writers who are willing to commit themselves to figures estimating the frequency of this occurrence. The percentages of frequency vary from 0 to 100 per cent. These reports extend over a period of 77 years, the first one being given by Dittrich in 1848. He placed the estimate at 5 per cent. During the next 34 years there are only four estimates, two of which are below 10 per cent., one at 40 per cent., and one at 100 per cent., which was given by Zenker. The last is the only 100 per cent. which appears in the literature. Within the next 18 years there were six more reports, all of which were under 15 per cent. This brings the reports up to 1900, making a total of eleven in all. The

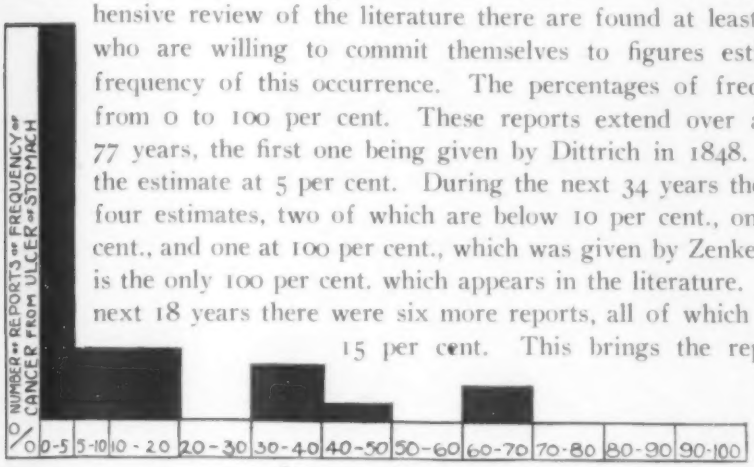

FIG. 2.—1916 to 1925.

majority of the work has been done since that time with perhaps the greatest amount in the decade between 1905 and 1915. Since 1900, there appear in the literature 71 articles in which an estimate is given, varying from 0 per cent. to 90 per cent. It is interesting to note that between 1905 and 1915 there are 38 articles, while between 1915 and 1925 there are 22 articles. (Fig. 1.) To analyze briefly the figures quoted in the former decade, we have of those under 5 per cent. fifteen, or 39 per cent., under 10 per cent. 19, or 50 per cent.; from 10 to 15 per cent. one and from 15 to 20 per cent. none, or under 20 per cent. twenty, or 52 per cent.; from 20 to 30 per cent. three; from 30 to 50 per cent. four, or under 50 per cent. twenty-seven, or 71 per cent. From 50 to 80 per cent. eleven, or 28 per cent. (Fig. 2.) In other words, there are approximately twice as many men believe that the development of carcinoma from ulcer is below the small number of 10 per cent. as there are those who believe the frequency is between the high percentages of 50 and 80. To analyze the whole number of reports found, which is 82, we find 39 per cent. of men estimating the frequency under 5 per cent., 50.6 per cent. under 10 per cent., as compared to 18 per cent. of men who estimate the frequency to be over 50 per cent. (Fig. 3.) Figures, in this case, of course, do not prove that the occurrence is necessarily low, but in the face of such strong evidence it is very difficult to believe that the frequency is anywhere near as high as some reputable authorities would have us believe.

The crucial point in the whole question of the frequency of occurrence of cancer from ulcer lies in the individual differences in the determination of the pathology. This involves the criteria upon which the diagnosis is made. Examination of about 150 articles shows a surprising lack of harmony in the criteria. Until pathologists and surgeons adopt a uniform standard for the interpretation of the microscopic picture, there will always be a wide diversity of opinion, and furthermore, until such an agreement is reached we shall not be in a position to say with approximate accuracy the frequency of development of carcinoma on an ulcer basis.

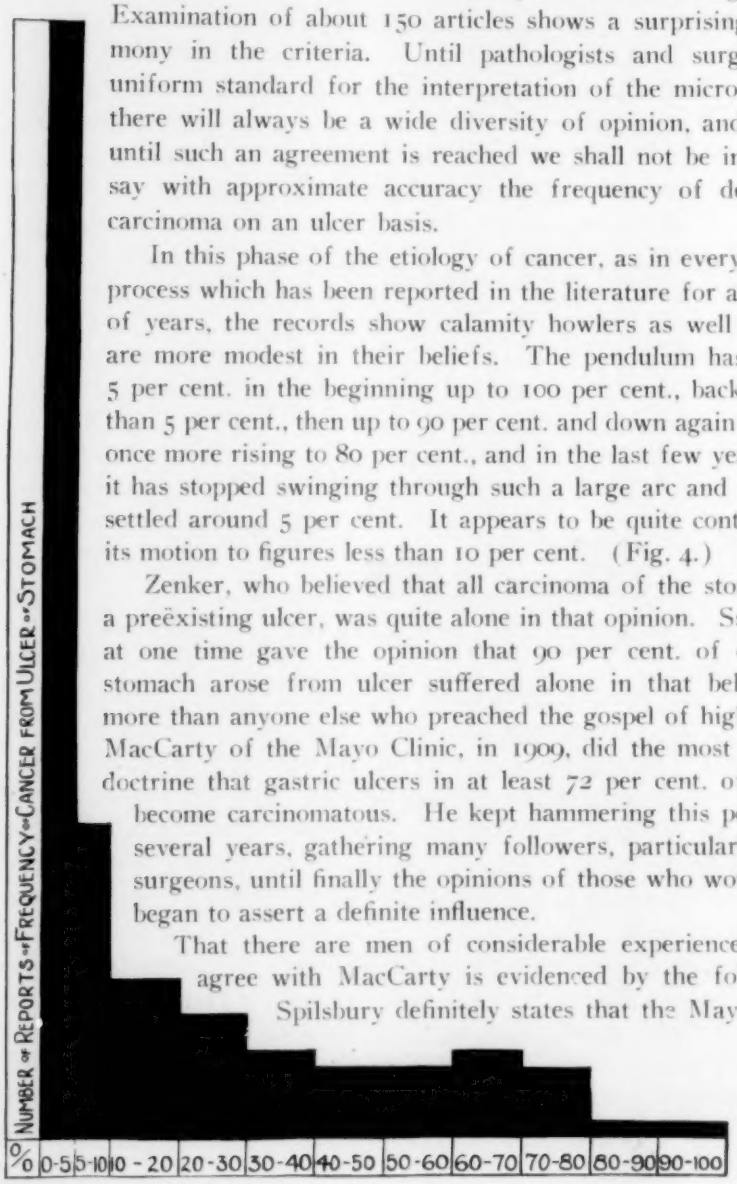

FIG. 3.—1843 to 1925.

In this phase of the etiology of cancer, as in every other disease process which has been reported in the literature for a great number of years, the records show calamity howlers as well as those who are more modest in their beliefs. The pendulum has swung from 5 per cent. in the beginning up to 100 per cent., back again to less than 5 per cent., then up to 90 per cent. and down again to 0 per cent., once more rising to 80 per cent., and in the last few years apparently it has stopped swinging through such a large arc and seems to have settled around 5 per cent. It appears to be quite content to confine its motion to figures less than 10 per cent. (Fig. 4.)

Zenker, who believed that all carcinoma of the stomach arose in a preëxisting ulcer, was quite alone in that opinion. Ssapeshka, who at one time gave the opinion that 90 per cent. of cancer of the stomach arose from ulcer suffered alone in that belief. Perhaps more than anyone else who preached the gospel of high percentages, MacCarty of the Mayo Clinic, in 1909, did the most to spread the doctrine that gastric ulcers in at least 72 per cent. of cases would become carcinomatous. He kept hammering this point home for several years, gathering many followers, particularly among the surgeons, until finally the opinions of those who would not be led began to assert a definite influence.

That there are men of considerable experience who do not agree with MacCarty is evidenced by the following facts. Spilsbury definitely states that the Mayo criterion of isolated cells detached from the regenerating epithelium and buried in the fibrous tissue is not necessarily correct. He goes further even, in pointing out that processes of irregular regeneration are mistaken for malignant transformation by many.

Aschoff, whose opinion is extremely valuable, does not state definitely the

percentage of occurrence, but does say, in 1911, that the transformation of a simple ulcer into cancer is not as frequent as it has been variously assumed.

Anschutz, in 1912, said that the Mayo group lay great stress on the history of preëxisting ulcer which in his opinion was of little value. MacCarty shows very pretty pictures and gives exact histological descriptions, but even then he cannot be convinced in this important question. He is not able to join in opinion with MacCarty that 70 to 80 per cent. of carcinoma develops on known ulcer basis, but gives as his own opinion that the number of cases that one can say with precision developed from an ulcer basis is very small. As late as 1920 he believes that the highest percentage of carcinoma from ulcer is from 3 per cent. to 5 per cent.

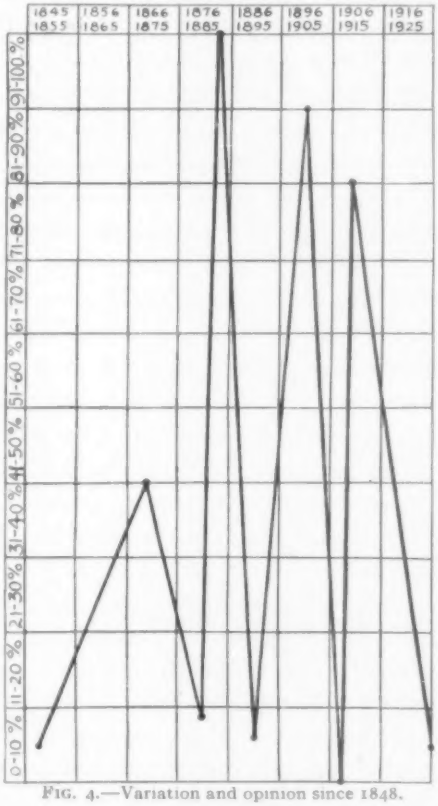

FIG. 4.—Variation and opinion since 1848.

Aaron, in discussing carcinoma of the stomach, quotes Wilson and MacCarty as concluding that practically all carcinomata develop on the site of a previous ulcerative lesion of the gastric mucosa and adds that this report is not in accord with his clinical experience. Aaron also quotes A. Kocher, who says that he has personally examined the Mayo specimens and is convinced that much of what they labeled cancerous degeneration of ulcers was in reality merely atypical proliferation of epithelium, or only epithelial changes in the progress of the ulcer and have nothing to do with carcinoma.

Ewing, in 1918, says that MacCarty uses as evidence of carcinoma, inflammatory hyperplasias and misplacement of gastric glands, which may well be grouped under precancerous conditions, but that is no evidence that they develop carcinoma.

Spilsbury and Ewing have both emphasized the observation that if the base of the ulcer is infiltrated with carcinoma the lesion has been carcinoma from the start.

Bartlett adds another observation which may well be included in the criteria. It is that in gastric ulcer the muscle coat is completely destroyed in the base while with carcinoma this but rarely happens; hence if there were well-defined portions of muscle in the base of a carcinomatous lesion, it is strong evidence that the neoplasm did not arise in the edge of an ulcer.

Konjetzny, in 1913, in speaking of MacCarty's work of 1909, says the description is so fragmentary and scanty, so purely subjective, that not in

a single instance does it suffice or satisfy even a moderate claim. As to the question how frequently does carcinoma develop from an ulcer, the work of MacCarty and Wilson is worthless.

As has already been pointed out, the percentage of frequency of carcinoma from ulcer varies from 0 to 100 per cent., according to the pathologists who have reported on this subject for the last 75 years. That there is such wide divergence of opinion is only evidence of the lack of standardization of criteria. In addition to the microscopic evidence we must examine the clinical aspects and attempt to bring them nearer together. The most important feature of the clinical side of the question according to some authorities seems to be the history of the patient, that is the evidence by symptoms that a gastric ulcer has existed for a certain period of time, usually more than five years, previous to the appearance of the typical gastric carcinoma picture. This particular point also seems to be somewhat in doubt. There are those who lay great stress upon the ulcer history and others who claim that it is very difficult to make a diagnosis of ulcer from the history, some who say even that any patient with gastric symptoms may be made to give practically an ulcer history by the clever presentation of leading questions. Then there is always the possibility of a typical gastric ulcer history really being that of duodenal ulcer.

Lockwood, in speaking of the 70 per cent. frequency of cancer from ulcer which is claimed by some, maintains that the pathological findings are at variance with the clinical observations, namely, that the history of preëxisting ulcer is not present in 70 per cent. of carcinoma cases. He finds 7 per cent. of cases with a suspicious history, while only 3 per cent. have a positive history. Lockwood also points out the change in the ideas of Mayo-Robson who in 1901 wrote, " It is, however, rare to elicit a history of very old standing stomach disorder. The first evidences of local disease appear suddenly in persons of perfectly sound health and robust digestion." In 1907, only six years later, Mayo-Robson writes, " In no less than 59.3 per cent. of carcinoma of the stomach on which I have performed gastro-enterostomy for the relief of symptoms, the disease having advanced too far for gastrectomy, the long history of painful dyspepsia suggests the possibility of ulcer preceding the onset of the malignant disease." Lockwood comments on the pretty rapid and radical change of ideas.

Moynihan, in 1909, says that two out of three cases of carcinoma operated by him had a history of previous ulcer. In 1906, he found in one group of 22 patients, 72.1 per cent. of ulcer preceding cancer. McDowell, in 1919, says that it seems probable that gastric cancer rarely develops except at the site of a previous ulcerative lesion of the mucosa and that the clinical and pathologic data of the development of gastric cancer on gastric ulcer are in close agreement with regard to, one, the average age of the patient at operation; two, the average period of previous history of ulcer; three, the average number of months of acute symptoms.

Taylor and Miller find a history of preëxisting ulcer in 17 per cent. of a group of 182 cases.

Osler in 150 cases found ulcer history in 2.6 per cent. and in not a single instance could it be positively diagnosed. Fenwick found 3 per cent. ulcer history in his cancer cases, Haberlin 2.3 per cent. and Eichhorst 2 per cent.

As evidence tending to show that cancer does not develop from ulcer with great frequency, we may briefly review those cases in which a gastro-enterostomy has been done for simple ulcer and the patients observed for

TABLE I.

Age Incidence.

Age	Cases	Per cent.	40 to 60	50 to 70	40 to 70
15–19	1	0.86			
20–29	4	3.44			
30–39	13	11.2			
40–49	18	15.5			
50–59	42	36.2	51.7		81.0
60–69	34	29.3		65.5	
70–79	3	2.5			
80–89	1	0.86			
Total...	116				

several years after. Paterson finds that death from carcinoma after gastro-enterostomy for simple ulcer is rare, in his own cases 1 per cent. Kocher in 50 cases of gastro-enterostomy for simple ulcer one to twelve years after found no cases of malignancy. He later adds 30 cases to the already published 50, making 80 in all, and still finds no case of carcinoma developing after operation for ulcer. Billeter, in reporting 122 cases of ulcer, had 6 deaths, 4 resections in which no malignancy was found, 112 gastro-enterostomies in which only one carcinoma developed after operation. Greenough and Joslin had one carcinoma out of 114 gastro-enterostomies, Hemmeter had three out of 232 gastro-enterostomies. Bamberg, in 1909, reported 1025 gastro-enterostomies for ulcer and found that 2.1 per cent. developed cancer subsequent to the operation for ulcer. Of 152 cases of gastric ulcer in which resection was done, 1.9 per cent. subsequently developed carcinoma. Gressot reports a percentage of 2.3 of carcinoma developing after operation for ulcer, presumably gastro-enterostomy. Sherren operated 200 cases of gastric ulcer, performing gastro-enterostomy, and in no instance did he find carcinoma developing after operation. Rehfus, in 1924, reports his percentage as one to two. Exalto, in 1918, found two out of 208 cases.

The group of cases here considered is that coming to the Surgical Service of the University of Michigan Hospital from 1916 to 1925. They include

only cases in which the facts have been demonstrated by operation and many of them checked by the pathological report. We are quite aware that this is not a large series of cases, but we think it justifiable to consider them particularly in their bearing upon the question of relation of ulcer to cancer.

Table I shows the age incidence and does not importantly depart from the figures of other observers. It shows, as have others, that the condition is most common at or after middle life, 51 per cent. of the cases falling between the ages of forty and sixty and 81 per cent. between the ages of forty and

TABLE II.

Duration of Symptoms According to Age of Patient.

	2 mo.	4 mo.	6 mo.	9 mo.	12 mo.	18 mo.	2 yr.	4 yr.	5 yr.	8 yr.	10 yr. & over	Not mentioned
Age	Duration of Time and Number of Cases.											
20–25				1	1			1				
26–30	1		1			1			1			
31–35	1		1		2							
36–40	1	1	3	1	5							
41–45	1	1	1	1	2				1			
46–50	3	1	2	1	1	1	2					
51–55	1	2	1	2	7	2	1	1		1		
56–60	3	4	4	4	4		2			1	1	
61–65	4	6	4	1	2	1	2				1	
66–70	2	2	2					1				
71–75			1									
76–80			2									
Total.	17	17	22	11	24	5	7	3	2	2	2	4-116

seventy. It is perhaps also worth while to point to the relatively large number of cases between thirty and forty, 11 per cent.

Table II shows the duration of symptoms and again departs in no important way from the accepted views upon the subject, namely, that the symptoms in cancer are notoriously of short duration as compared with the cases of non-malignant ulcer. The vast majority of these patients had symptoms for less than one year and a very considerable proportion had symptoms for six months or less.

History of Ulcer.—Some discussion might readily arise over what constitutes a history justifying the diagnosis of peptic ulcer. Some observers would take the view that any history showing pain in the upper abdomen, whether or not related to food, whether or not coming in attacks, might be regarded as evidence of ulcer. It has seemed to us that we were required to

at least attempt to be a little more critical and we have regarded the phrase "a history of ulcer" as requiring us to show pain referred to the upper abdomen bearing some demonstrable relation to the taking of food and continuing over a reasonable period of time. Judged in this way there are only nine cases in this series which could be regarded as having a history of ulcer. (Table III.)

Of these some had a surprisingly long history, one of them extending over thirteen years, though only acute during the final twelve months. One lasted

TABLE III

History of Previous Ulcer in 112 Cases

Cases with History of Previous Gastric Disturbance..... 9—8.3 per cent. of 112.

Number of Cases	Duration
1	3½ years
2	4 years
2	5 years
1	7 years
1	8 years
1	10 years
1	13 years
9	

Cases without History of Previous Gastric Disturbance....103—91.7 per cent. of 112
Cases in which Duration of symptoms were not mentioned. 4

116

ten years; one, eight years; one, seven years; two, five years; two, four years, and one, three years and a half. Here is a group of roughly 8 per cent. of our cases in which the history strongly suggested ulcer of the stomach and in which cancer was ultimately found. It is unfortunate that in this group we have only fifty-six cases in which the complete pathological study was made.

Various writers have put forward the view that the history was an important part of the evidence leading to the opinion that cancer was a relatively frequent result of ulcer. We confess that this does not appear to us logical. The short duration of the history in most cases of cancer cannot, we think, be properly held to bear any known relation to the disease itself. It is notorious that in other parts of the body at least, cancer, particularly in elderly people, is a relatively slow-growing process and it does not seem to us likely that the massive tumors which occur in some of these patients with a very short history of discomfort could have been produced in that short period. We doubt whether the duration of symptoms in the cases of cancer has any relation to the duration of the growth. It is of course possible that the symptoms are chiefly produced by surface loss of substance and that a malignant process developing in the stomach wall which does not result in loss of substance might go on for a considerable period without producing symptoms. There is another reason for skepticism in regard to the value of

so-called history of ulcer, namely, that it is not uncommon to see patients with an almost classical history of ulcer in whom no ulcer can be demonstrated to exist. It is certainly true that other conditions may produce symptoms which at least, as interpreted by the patient, would suggest ulcer. We are inclined to take the view that the history is a relatively unreliable basis for judging the relationship between ulcer and cancer.

Location of the Growth.—Some interest attaches to the position of the growth, particularly in relation to the discussion of etiology. In our series

TABLE IV.

Location of growth	Number cases	Per cent.	
Pylorus	55	56.1	of 98 cases
Diffuse	16	13.8	of 114 cases
Lesser curvature	15	11.7	of 98 cases
Cardia	9	9.0	of 98 cases
Both walls	8	7.1	of 98 cases
Posterior wall	5	5.1	of 98 cases
Greater curvature	4	4.0	of 98 cases
Anterior wall	2	2.0	of 98 cases
Not mentioned	2		
	116		

sixteen cases should be excluded since the growth was so diffuse as to make it impossible to say where it had begun, and two should be excluded since location is not mentioned. Of the remaining ninety-eight, fifty-five occurred at the pylorus, fifteen upon the lesser curvature, nine at the cardiac end, eight on both walls, five upon the posterior wall, four upon the greater curvature, and two upon the anterior wall. These figures are somewhat less striking than those of many observers reporting larger series. In general, the common figures show that 60 per cent. of the cases of carcinoma occur at the pylorus and about 12 per cent. of the cases of ulcer, while 60 per cent. of the ulcers occur upon the lesser curvature and only 12 per cent. of the cases of carcinoma. In general our figures agree with other observers and tend to show that from this view there is no very striking ground for the assumption that cancer commonly or generally originates on the basis of ulcer. (Table IV.)

In our series the type of cancer is known in fifty-six cases. Of these twenty-five were adenocarcinoma, nineteen were scirrhous carcinoma, seven were mucoid carcinoma, three were medullary carcinoma and two were colloid carcinoma.

Evidence of Preëxistent Ulcer as Shown by the Pathological Report.—It may perhaps be suggested that no clinician ought to venture into the dis-

cussion of the pathological evidence of previous ulcer and certainly any clinician so venturing takes his life in his hands. As we have already shown, opinion in regard to the frequency of ulcer as a forerunner of cancer has varied through very wide limits and this variation of opinion has occurred both among the clinicians and the pathologists. It seems to us that the question turns largely upon the criteria which are laid down as diagnostic. It is obviously possible to lay down criteria by the result of which the vast majority of cases of chronic ulcer, whether of the stomach or elsewhere, may be adjudged to be showing precancerous tendencies. MacCarty has perhaps taken the broadest view of the evidences which should be adjudged to indicate either the presence or the imminence of cancer. He has had at his disposal an immense material and his opinions are clearly entitled to weight not only on this account, but on account of his very careful and thorough study of the subject. He has been the outstanding advocate of the view that a large proportion of cases of cancer had as their cause a preëxisting ulcer. From his many contributions to this subject it is difficult to pick out excerpts which will fairly represent his criteria. The following quotation from his publication in 1909 shows his views at that time:

Infiltration after Proliferation:

In scirrhous type—fibrous tissue forms around epithelial cells which are proliferating.

Cancer develops in scar tissue in some cases.

Bands of scar tissue with epithelial cells included suggest early cancer.

Ulcer usually exists for years before cancer develops—in a group of cases.

Large ulcers with scar tissue centres and overhanging borders deep in the bases of which cancer is present, in almost every instance have originated on the lesser curvature, the usual site of gastric ulcer. Further, history of ulcer extends years back before relatively short period when history became that of cancer.

In 1910:

Inflammatory hyperplasia and malignant hyperplasia are indistinguishable.

Hyperplasia is forerunner of malignancy.

Cancer is a malignant hyperplasia which also varies in degree, and some of the degrees so far as morphology is concerned are indistinguishable if not identical.

In 1915:

The epithelial cells of the glands in some ulcers lose their cuboidal or columnar shape and regularity of size and arrangement. They become oval or round and the nuclei larger and more distinct. The exact origin is unknown since in gastric glands there are not two distinct rows of cells normally present as in breast, prostate, skin, etc.

Various degrees of intraglandular morphological changes are found in the borders until the cells become indistinguishable from cancer cells. When such a condition is found, careful search frequently demonstrates a lack of demarcation between gland and stroma, and epithelial cells may be seen in the stroma, the latter condition being accepted by general pathologists to be the histological criteria of cancer.

When cancer is definitely present the intraglandular cells always present what is described as secondary hyperplasia in other organs.

In the production of this epithelial hyperplasia, there is an attempt on the part of nature to reproduce the epithelial lining of the glands. In this attempt there is failure to completely differentiate the cells with the coincidental picture of secondary hyperplasia, the cells of which differ from cancer only in position.

From these facts one may clearly see that the gastric cancer cell arises from intraglandular hyperplastic cells of the mucosa, and represents a malignant end-stage of a process of hyperplasia of normal cells.

MacCarty in 1909 gives cancer ex ulcero as 71 per cent.

MacCarty in 1914 gives cancer ex ulcero as 69 per cent.

HAUSER is commonly thought of as having early dealt with this question of criteria and has been much quoted in these discussions. He has the following to say on this subject:

Deep, sharply cut excavation, overhanging proximal edge, firm, fibrous base and often the extension of cicatrix to surrounding organs are satisfactory evidences of the long existence of a typical peptic ulcer. The carcinoma has usually appeared at one or more points, usually distal, sometimes fused and causing induration and fixation of the edge. Outlying islands of polypoid adenoma or adenocarcinoma are not infrequently observed.

The edges are markedly hypertrophic. Cancer changes are most marked at the line of the ulcer and extend with diminishing intensity for a distance of one-half to one cm. over the outlying mucosa, the infiltration involving the peripheral submucosa and muscularis, while the indurated base is free from infiltration.

EWING lays down the following criteria and also states his conclusions in regard to the relation of ulcer to cancer.

1. The great majority of ulcerative lesions of the stomach fall into two classes:
   A. Ulcerating cancers.
   B. Simple peptic ulcers.

2. In certain peptic ulcers a large part of the gastric mucosa is the seat of glandular hypertrophy with atypical changes in isolated glands and interstitial growth of connective tissue causing some derangement of glands. This is not secondary to ulcer, but may well predispose to ulcer. This may serve as a source of error in interpreting atypical overgrowth on ulcer edge.

3. Deep excavations may occur in portions of established carcinoma, especially in the pylorus, where powerful muscular contractions tend to cause hernias of the infiltrated and weakened muscle tissue.

4. Gastric digestion may strip a primary carcinoma down to muscularis or deeper, leaving no trace of carcinoma over base, but only peripheral ring of tumor tissue which is protected by mucosa.

5. When ulcer base is uniformly infiltrated with carcinoma, the condition is difficult to reconcile with an origin from the edge. Hence, great importance would seem to attach to the condition of the base of the ulcer in the diagnosis between primary and secondary carcinoma.

6. The occurrence of atypical epithelial proliferation in the glands on the edge of the ulcer is not sufficient evidence that the lesion is going on to cancer.

CONCLUSIONS

Carcinomatous transformation of a peptic ulcer does not exceed 5 per cent. The proportion would be smaller if only the cases were included where the evidence is demonstrable, *viz.*, a long history of ulcer—the limitation of the tumor to isolated foci or one portion only of the ulcer—freedom of the base from infiltration.

SPILSBURY, 1922, has the following to say:

Discusses the diagnosis of gastric ulcer under two heads:

1. Destruction.
2. Regeneration.

At this stage there are commonly found at the edge of the ulcer, gland cells which

have penetrated deeply into the scar tissue and are cut off from the regenerating glands. They may show a typical glandular arrangement, or may form narrow solid columns of cells. Isolated cells are also seen. It is these *cells* detached from the regenerating epithelium and buried in the fibrous tissue of the ulcer which are referred to as precancerous, and from position and irregular arrangement regarded by *others* as indicating a malignant transformation in the ulcer.

This is the Mayo criterion—not necessarily correct.

Displaced and buried epithelial cells are not peculiar to healing peptic ulcer. Found anywhere in skin or mucous membrane, ex. varicose ulcer of leg.

If cancer develops in a peptic ulcer, it must do so from actively growing and regenerating mucous membrane at the margin of a healing ulcer or from buried cells mentioned above. Such might spread from margin into tissue at base or might spread into normal stomach wall, spreads here more rapidly, hence ulcer will exhibit structure of peptic ulcer, but with a more pronounced thickening of margin on one side. There may be superficial ulceration of indurated area, growth may fungate, forming polypoid or large, soft, irregular tumors; beyond the apparent margin of the tumor separate nodules may be found in the stomach wall. On microscopic examination the bulk of the original peptic ulcer will be found to consist only of fibrous tissue and to be free from cancer. These have been encountered occasionally and described as malignant transformation in a peptic ulcer.

Processes of irregular regeneration mistaken for malignant transformation by many.

Estimate from above criteria (same as Ewing) certainly not more than 5 per cent. of peptic ulcers of the stomach, probably not more than 1 to 2 per cent. develop secondary malignant disease.

When dense fibrous tissue of base is infiltrated everywhere with cancer cells regard such a tumor as a primary cancer with secondary ulceration.

Malignant transformation of a peptic ulcer must be an uncommon event.

At our request PROFESSOR A. S. WARTHIN has set down for us the following as the criteria which influence him in coming to an opinion:

Criteria for diagnosis of carcinoma arising in a chronic peptic ulcer: There must be convincing evidence of the existence of an older ulcer in the presence of an induration or cicatricial fibrosis extending through the stomach wall with characteristic sclerosis of the blood-vessels—the greater part of this cicatrix being entirely free from carcinomatous infiltration—the latter being limited to the borders or surface of the ulcer—the carcinoma must be a relatively early development, infiltrating the ulcer-scar to but a slight extent, so that there can be no doubt that the fibrosis is the result of the healing of an older ulcerative process and not secondary to the carcinoma. If the induration is the result of a primary carcinomatous ulcer, it will be infiltrated throughout with cancer-cell nests. It is important, however, that no errors be made in the interpretation of regenerative gland-formations and proliferations at the sides or base of an ulcer. These have undoubtedly been mistaken by some pathologists for evidences of malignancy. No diagnosis of cancerous or pre-cancerous states can be made from the characteristics of individual cells of such regenerative conditions, either in size, form or staining qualities of nuclei or cytoplasm. The diagnosis of carcinoma depends wholly upon the presence of free-growing cells in the tissue-spaces, infiltrating the scar tissue, producing a secondary inflammatory reaction in the latter and presenting the appearances of mature cancer nests, and not connected (in serial sections) with the normal glands at the border of the ulcer. In serial sections the continuity of regenerative proliferations with the bordering epithelium can always be demonstrated; in the cancer no continuity between normal gland epithelium and the carcinoma can be shown. A destructive infiltration of the mucosa at the border of the ulcer with cords and masses of epithelial cells more or less atypical, growing without relationship to a basement membrane, should be interpreted as carcinoma.

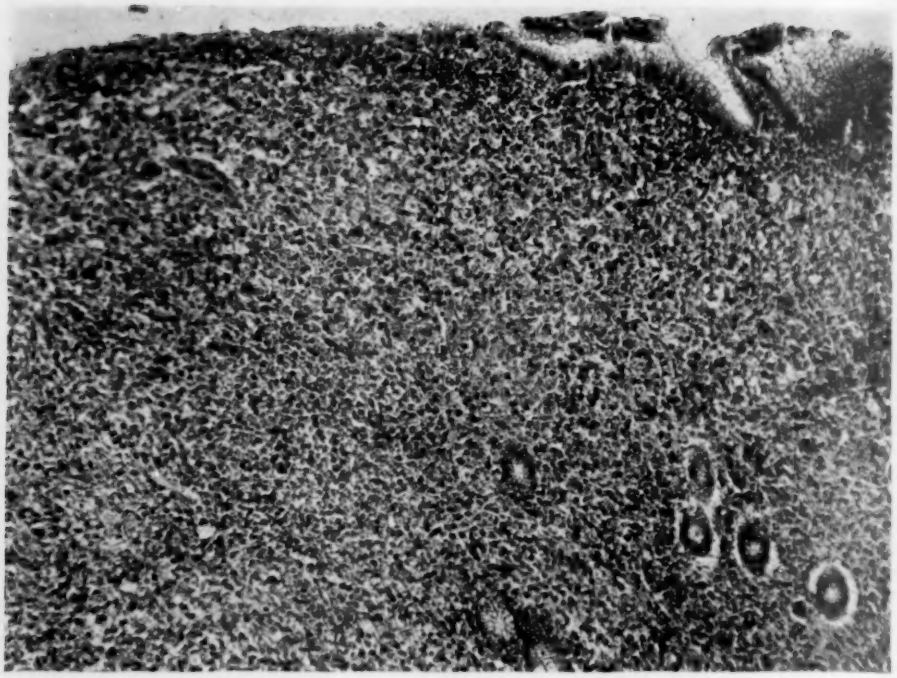

FIG. 5.—Case I, 1329-4, J. G. Scirrhous ("signet-ring" celled) carcinoma infiltrating mucosa at border of chronic peptic ulcer.

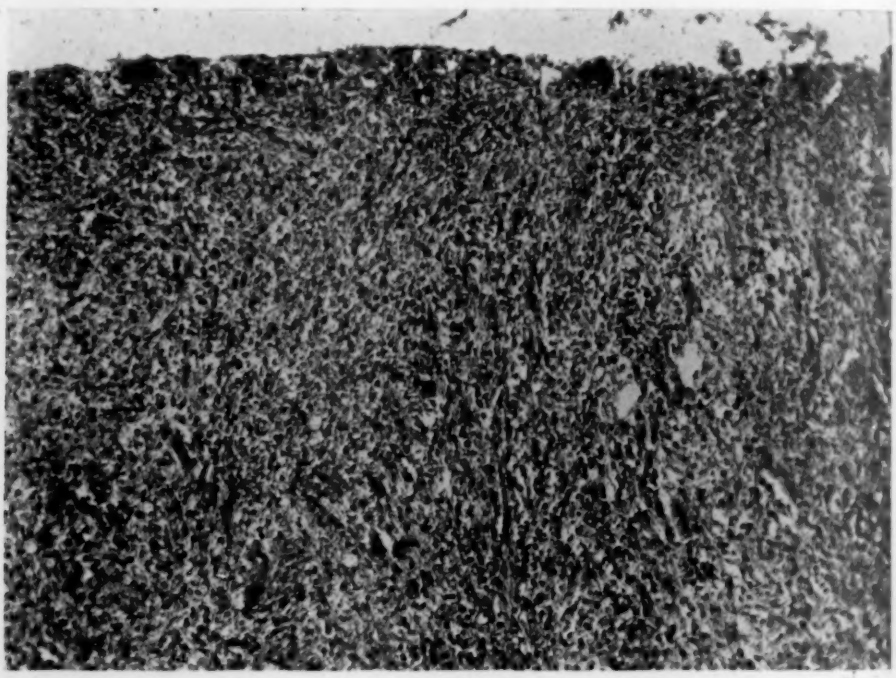

FIG. 6.—Case I, 1329-7, J. G. Small-celled ("signet-ring" scirrhous) carcinomatous infiltration of base of chronic peptic ulcer, near border

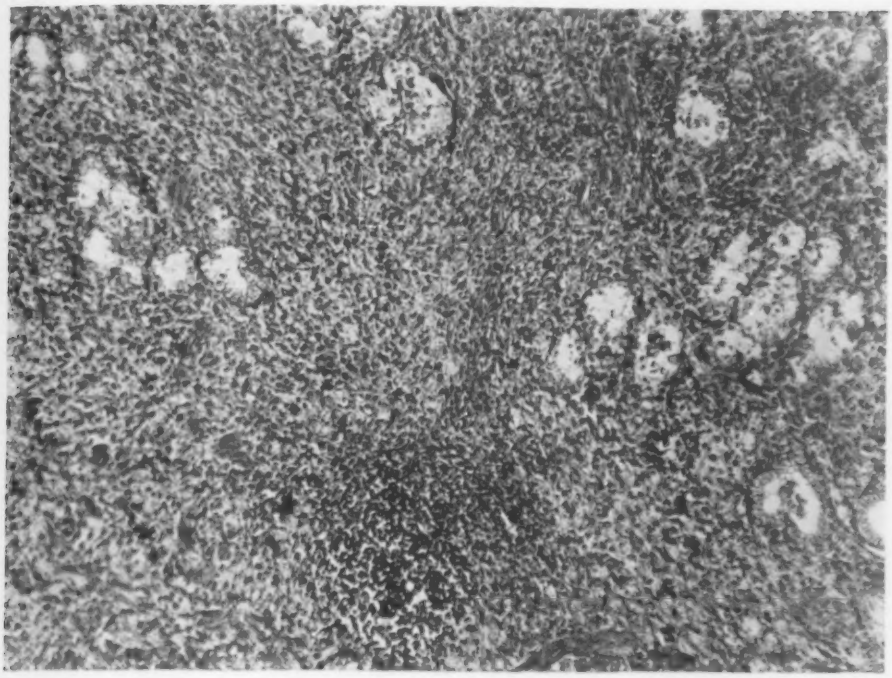

FIG. 7.—Case I, 1329-7, J. G. "Signet-ring" scirrhous carcinomatous infiltration of mucosa near border of chronic peptic ulcer. Remains of older glands showing mucoid degeneration.

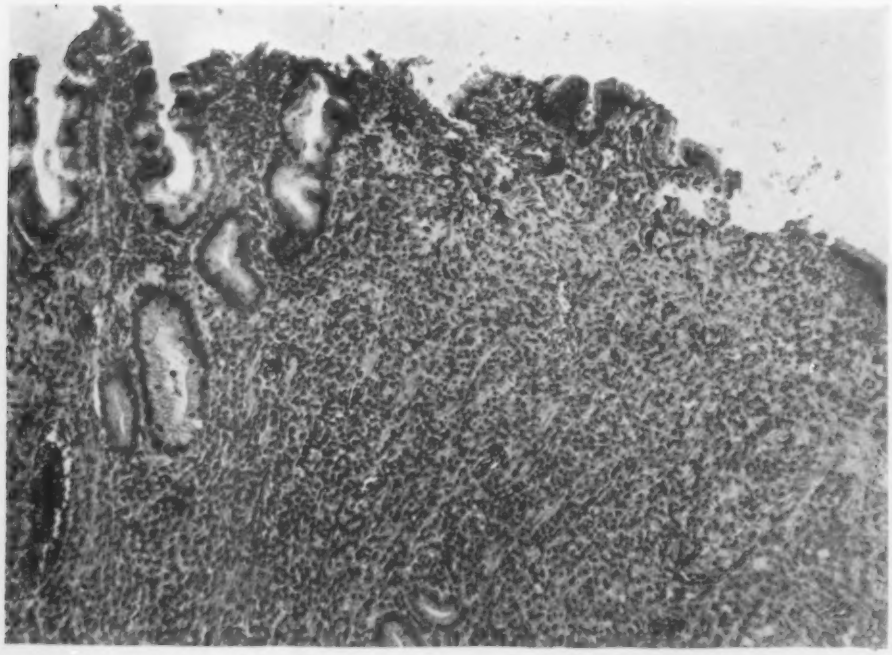

FIG. 8.—Case II, 1607-AA, C. C. Edge of chronic peptic ulcer with early diffusely—infiltrating scirrhous carcinoma developing on one side of ulcer. Infiltration of border of ulcer with small round carcinoma cells, some showing "signet-ring" mucoid degeneration. Carcinoma arising in primary peptic ulcer.

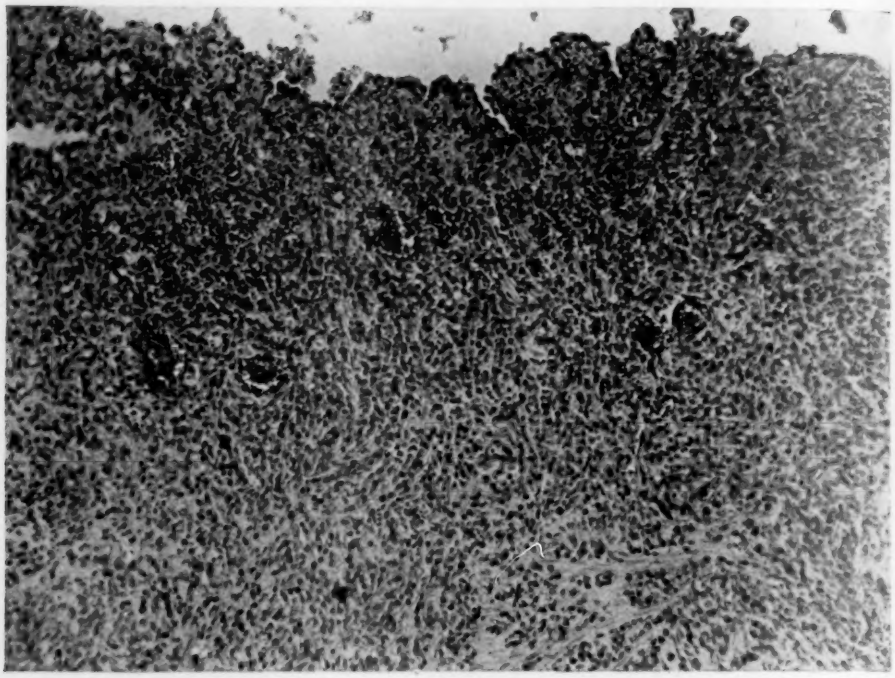

FIG. 9.—Case II, 1607-AA, C. C. Base of ulcer near carcinomatous border, showing cords of small round carcinoma, cells infiltrating scar tissue. Carcinoma arising in primary ulcer.

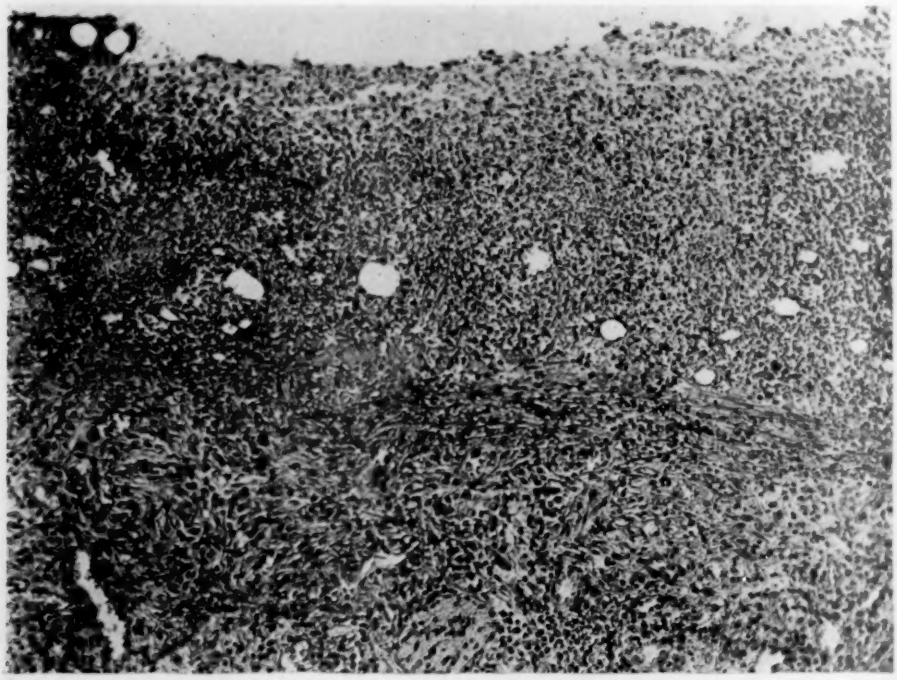

FIG. 10.—Case II, 1607-AA, C. C. Base of centre of ulcer above, exudate on floor of ulcer; below scar-tissue infiltrated with plasma-cells, lymphocytes and leucocytes. No carcinoma cells.

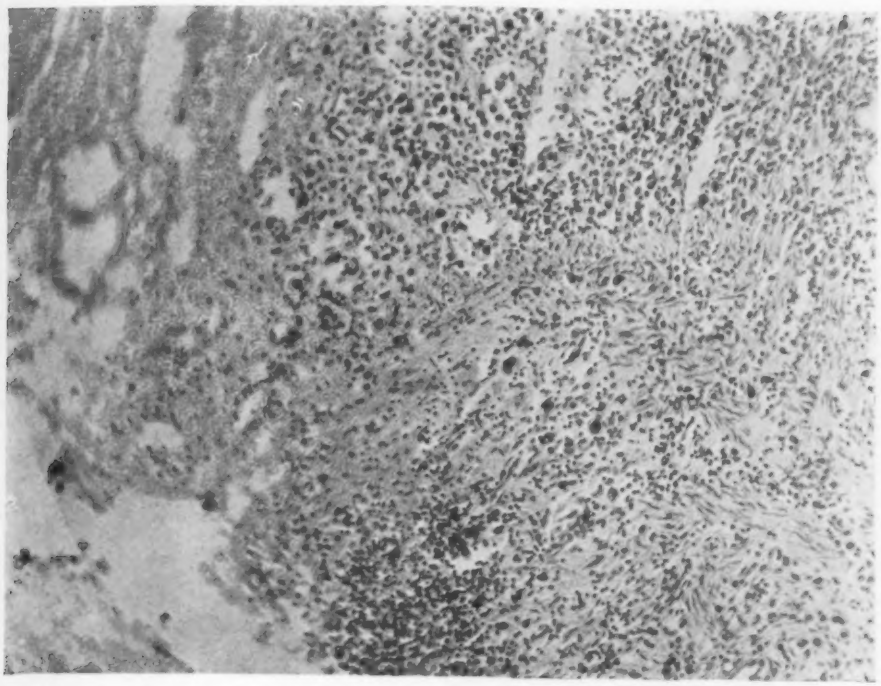

FIG. 11.—Case III, A-116-AB, V. B. Scirrhous carcinoma at border of older gastric ulcer.

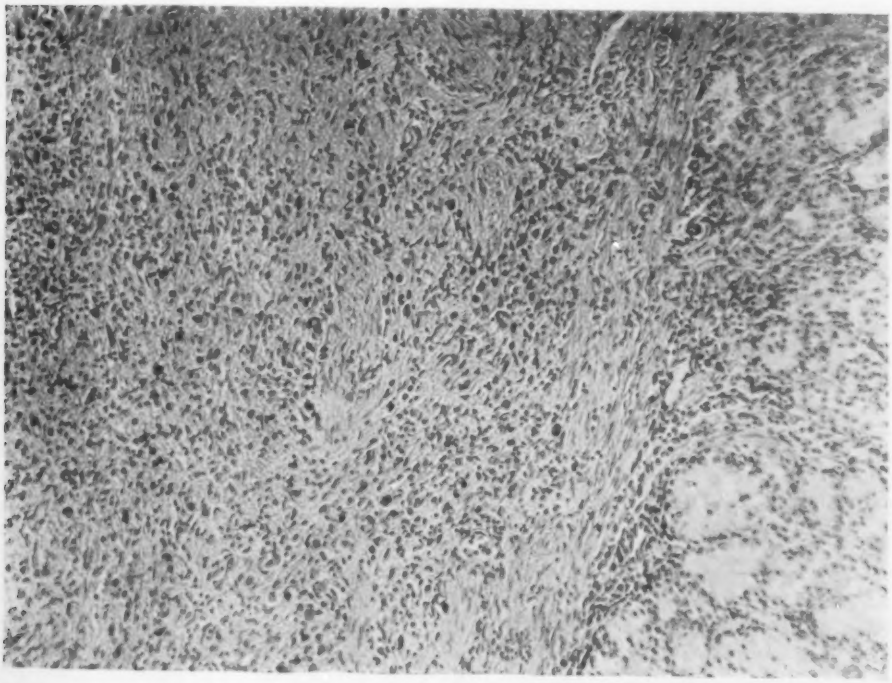

FIG. 12.—Case III, A-116-AB, V. B. Scirrhous carcinoma infiltrating gastric submucosa of border of older ulcer.

Of the cases in our series there are fifty-six in which the whole region was at the disposal of the pathologist. We have not included cases in which only a portion of the specimen was available, since it might easily be suggested that some other portion not at the disposal of the pathologist might have shown evidence of cancer. In this group there are five cases in which there is clear evidence of both peptic ulcer and cancer and using the criteria laid down above, Professor Warthin has come to the conclusion that they are true instances of cancer developing secondary to chronic ulcer. This would appear to require the admission that cancer is a definite result of ulcer in a certain proportion of cases.

The following is a brief abstract of these cases:

CASE I.—J. G., male, fifty-seven. No history of previous ulcer. Duration of symptoms, two months. Loss of weight, twenty pounds. Palpable mass in epigastrium. Operation: Partial gastrectomy. Pathological report: Scirrhous carcinoma of the stomach. Chronic peptic ulcer. Base of ulcer shows no carcinomatous infiltration, but the stomach wall and the borders do.

CASE II.—C. C., male, forty. No history of previous ulcer. Doubtful loss of weight. Partial gastrectomy. Pathological report: Very severe chronic hyperplastic catarrh. Two small subacute ulcers with a little island of preserved mucosa between them. These are relatively recent. The induration is still quite cellular and extending only to the muscles. The mucous membrane on one side is very atypical. The gland cells are small and infiltrate the stroma, and in one place extending through the mucosa. Early scirrhous carcinoma. In the other side of the ulcer there is also a group of carcinoma cells showing mucoid degeneration with signet-ring cells. The ulcer here has involved the carcinoma. There is no deep infiltration of the wall and this is about as early a stomach cancer as we have ever seen.

CASE III.—V. B., male, fifty-five. Entered on account of abdominal pain. Eighteen months' duration. No previous history suggesting ulcer. Loss of weight, twenty-five pounds. Operation: Partial gastrectomy. Pathological report: On the lesser curvature just above the pyloric opening on the posterior wall of the stomach there is an ulcer 8 cm long by 4 cm. wide with definite borders. The floor is irregular and at its lowest part there is a feeling of induration imparted to the examining finger. Edges appeared firmer in consistency than the floor. The depth of the ulcer is 5 mm. No induration or infiltration outside of it. Numerous small enlarged glands found along the greater curvature. Decided feeling of infiltration around the pyloric orifice. Microscopic examination: Old chronic peptic ulcer of large size. Marked fibroid. Induration of base. At border of ulcer is large area of scirrhous carcinoma infiltrating the mucosa and submucosa and into the muscular coats. No carcinoma at base or at other border. A carcinoma developing at the border of a chronic peptic ulcer. Mucosa shows chronic catarrhal gastritis. Lymphatic glands show atrophy and chronic passive congestion. Œdema. Early metastasis of carcinoma.

CASE IV.—W. C. G. The three photomicrographs shown below demonstrate the mistake that might be made in diagnosing carcinoma arising from chronic gastric ulcer.

CASE V.—J. J. V., male, thirty-nine. Enters on account of abdominal pain. No previous history of ulcer. Duration of symptoms twelve months. Loss of weight, twenty-five pounds. Operation: Partial gastrectomy. Pathological report: Chronic catarrhal gastritis. Large chronic peptic ulcer with dense inflammatory base. At the margin of the ulcer there is an adenocarcinoma which in its older portions shows the structure of an adenocarcinoma mucosum. This is apparently another example of the development of a carcinoma near the margin of a chronic ulcer. Two small lymph-nodes show no metastasis. The carcinoma is so well advanced, however, that we believe metastasis has probably taken place.

FIG. 13.—Case III. A-116-AB. V. B. Scirrhous carcinoma infiltrating cicatricial tissue of floor of ulcer at one border of the older ulcer. Carcinoma secondary to ulcer.

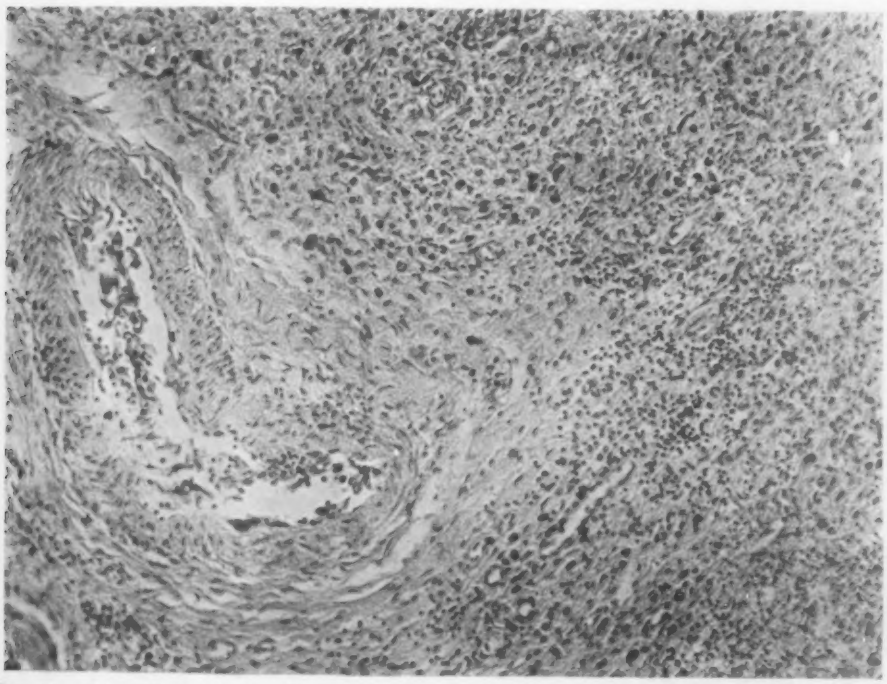

FIG. 14.—Case III. A-116-AB. V. B. Scirrhous carcinoma infiltration of subserosa at border of chronic peptic ulcer. Carcinoma arising in older ulcer and infiltrating floor and border of ulcer.

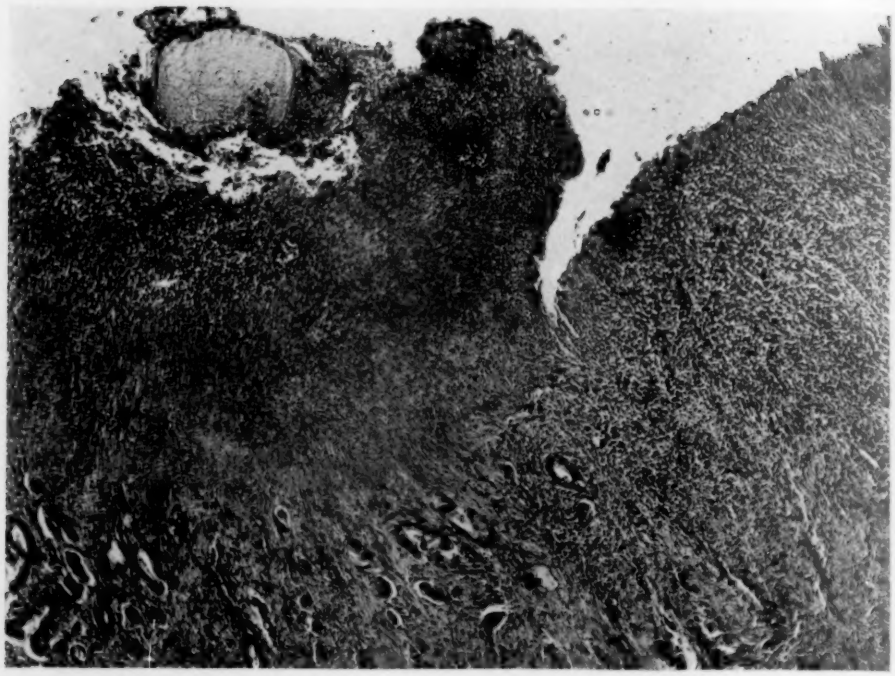

FIG. 15.—Case IV. 2530-AB. W. C. G. Low-power view of ulcerating adenocarcinoma. Ulcer is primarily carcinomatous.

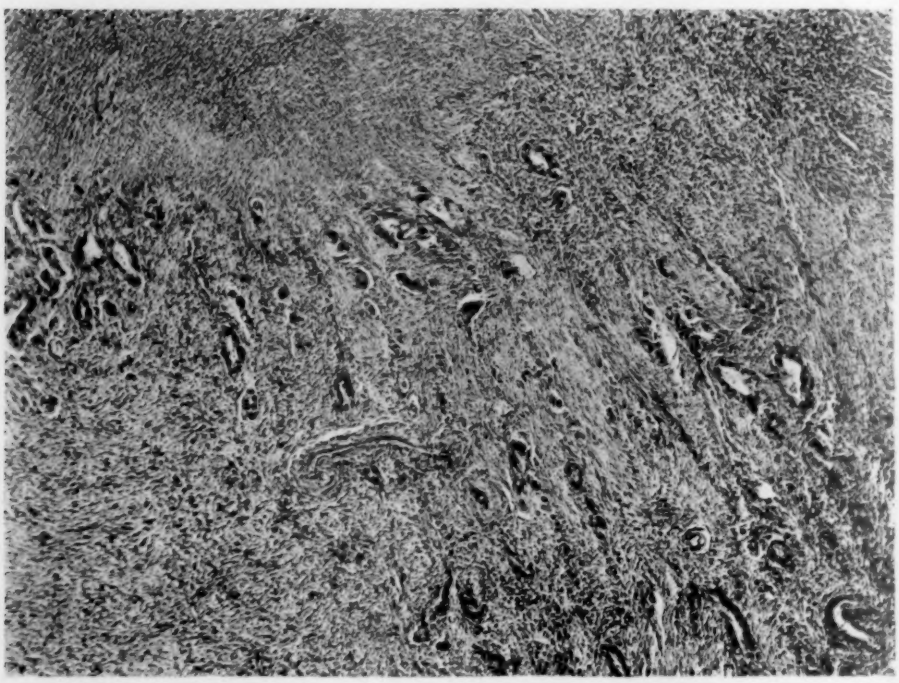

FIG. 16.—Case IV. 2530-AB. W. C. G. Floor of ulcer near opposite border from that seen in preceding adenocarcinomatous infiltration. Primary ulcerating adenocarcinoma.

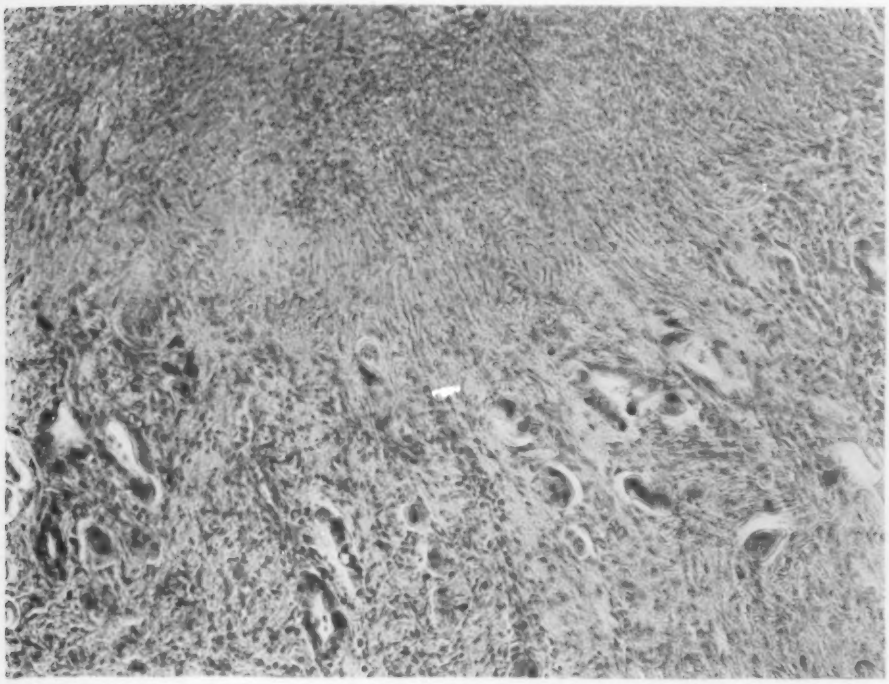

FIG. 17.—Case IV, 2530-AB, W. C. G. High-power view of preceding adenocarcinomatous ulcer.

FIG. 18.—Case V, 4266-AB, J. J. V. Edge of chronic gastric ulcer. Adenocarcinomatous border. Atypical, hyperchromatic gland tissue infiltrating border of ulcer. Floor of ulcer showed no carcinoma. Primary adenocarcinoma developing in border of chronic ulcer.

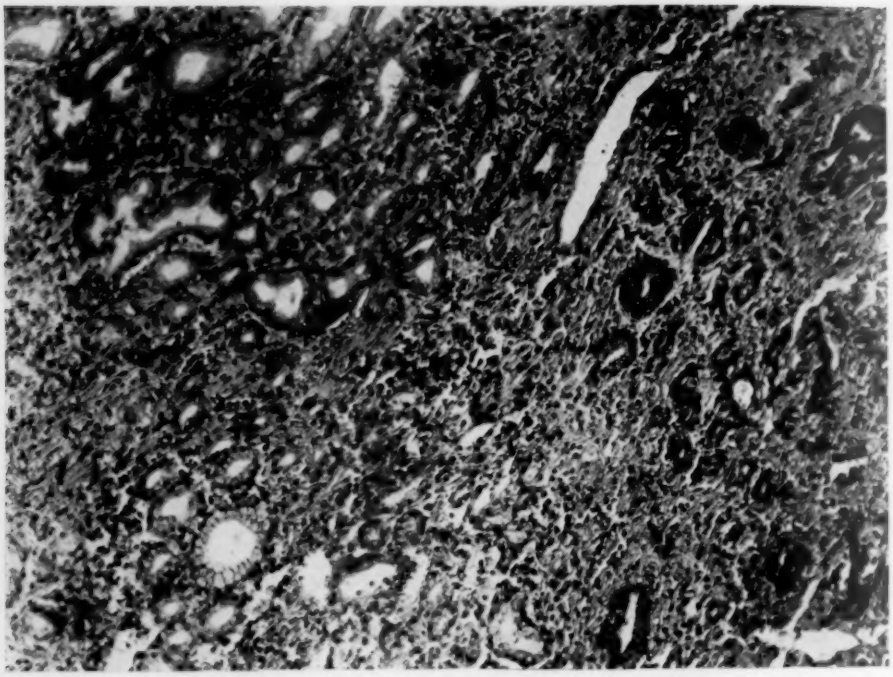

FIG. 19.—Case V, 4266-AB, J. J. V. Border of same ulcer as in preceding, a little farther from the ulcer, showing adenocarcinomatous infiltration of mucosa.

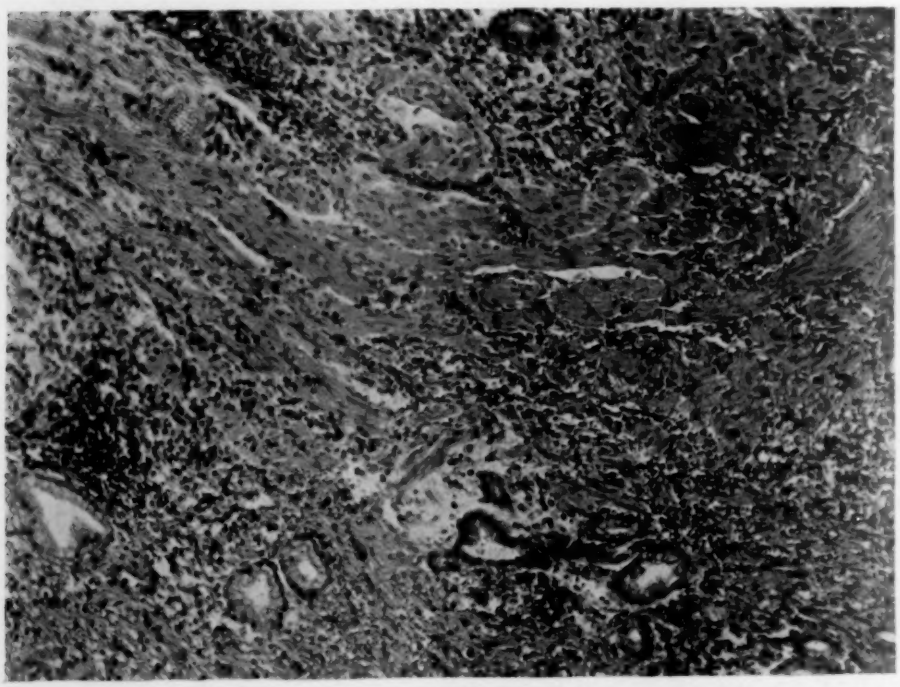

FIG. 20.—Case V, 4266-AB, J. J. V. Adenocarcinomatous infiltration of muscularis at border of chronic ulcer. Carcinoma arising at border of ulcer.

CASE VI.—W. H. S., male, seventy. Several years of indigestion. Possible ulcer history. Acute pain two months. Loss of weight, ten pounds. Operation: Partial gastrectomy. Pathological report: A scirrhous carcinoma arising from scar of old peptic ulcer. The carcinoma is rather superficial in the mucosa, but shows some infiltration into the submucosa and muscularis. The greater part of the induration due to the old chronic ulcer.

In some of the literature on the subject there appears to be confusion as to precisely what is being discussed. The most important question at issue appears to us to be not the proportion of cases of cancer in which ulcer has previously existed, and to which the cancer may be adjudged to be secondary, but what proportion of cases of chronic peptic ulcer of the stomach are likely to show malignant changes after a term of years. Now obviously the proportion of cases of cancer showing evidence of previous ulcer bears no relation to the whole number of cases of ulcer upon which cancer ultimately develops. This is a very difficult subject upon which to get convincing evidence. The best evidence obviously would be a collection of a large number of cases of demonstrated ulcer which after a term of years were known with equal certainty to have developed cancer. The literature on this point is not large and the relatively small number of cases which have been reported throws little light upon the proportion.

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PAPILLOMATA OF THE LARGE BOWEL*

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While the incidence of benign adenomata and papillomata of the large bowel is not great, they occur more frequently than any of the other benign tumors. There has been a rather sharp distinction drawn between the clinical and histological characteristics of adenomata and papillomata of the large bowel. Adenomata, found most often in childhood, also occur in adults as pedunculated mucous covered polyps with a smooth or finely lobulated surface. Occasionally they are found in the sigmoid as single tumors and reach a size sufficient to partially occlude the lumen of the bowel or become the apex of an intussusception. A condition of multiple polyposis is occasionally observed where hundreds of adenomata of varying size and attachment involve the whole large bowel. This condition has been well described in literature and the dangerous anæmia and tendency to malignant degeneration of the tumors have been emphasized. In addition to true adenomatous polyps, inflammatory polyps may develop in the base of amœbic ulceration or in hyperplastic tuberculous ulceration of the large bowel. These inflammatory polypi resemble neoplastic adenomata both in form and attachment, but may be differentiated by microscopic examination.

Incidence of Papillomata.—Papillomata or villous tumors of the large bowel have been described in occasional reports and are mentioned briefly in text-books.[1] A scarcity of the literature on the subject is no doubt in part due to the fact that no one observer has been privileged to observe a large number of instances of papillomata of the large bowel. Rotter [2] and Goebel [3] in the German literature, and Quenu and Landel [4] in the French literature have critically considered these tumors especially as to their potential malignancy. Allingham in his text-book of 1882, mentions fourteen cases, including those observed by Quain, who is credited with having first called attention to this type of tumor in the literature. Goebel, in 1913, collected seventeen cases described in the literature in addition to the forty that Rotter had reported. Since 1913, in a rather careful search, only six additional case reports were encountered. Undoubtedly other papillomata of the large bowel have been observed, but no record of them has been made.

While it is evident that papillomata of the large bowel are not common, they are nevertheless of importance from a diagnostic and surgical pathological point of view, due to their position in tumor classification as a precancerous lesion.

Symptomatology and Diagnosis.—These tumors are almost exclusively found in adults. If the papilloma occurs in the rectum, bleeding of bright red blood at the time of bowel movement is the most prominent symptom. If

* Read before the American Surgical Association, May 4, 1925.

this bleeding persists unchecked a secondary anæmia supervenes. In one patient observed the hæmoglobin dropped to 28 per cent. The bleeding, which may take on the character of a hemorrhage at times is not accompanied by the presence of pus in the stool, and this is a characteristic difference from carcinoma of the bowel. If the tumor is attached low in the rectum, it may prolapse and be reduced with more or less difficulty. A true prolapse of the rectum may be induced by the tumor which occupies the apex of the prolapsed bowel. Due to the large secreting surface of the tumor, a great amount of mucous is formed which may be passed at bowel movement or find its way out on the skin by leakage through the sphincter muscles.

If the papilloma occurs at the recto-sigmoid junction or higher in the large bowel, the bleeding is more likely to be intermittent and come in attacks. This is probably due to the lessened mechanical irritation of the soft tumor mass by contents of the bowel. If the papilloma reaches considerable size, constipation develops and a filling defect of the large bowel is seen which looks much like the filling defect in an early carcinoma of the colon (Fig. 4).

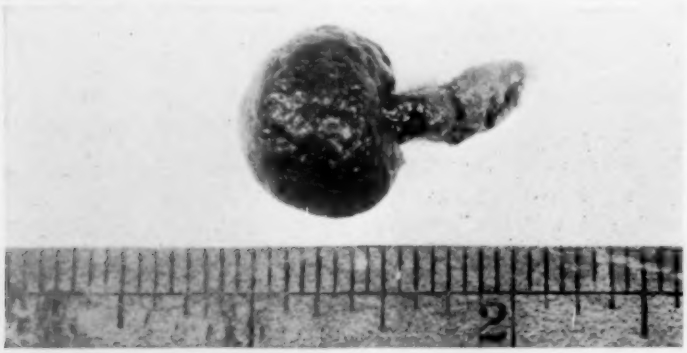

FIG. 1.—Simple pedunculated adenoma of the rectum, from a male aged twenty-five years.

The course of these papillomata may include several years with long periods of freedom from symptoms. The general health of the patient may be but little impaired. Pain is usually absent. These considerations are important in a differential diagnosis from cancer of the bowel. At the conclusion of the article, case reports will be given illustrating these points.

Pathology.—Papillomata of the rectum and colon correspond very closely in the gross appearance and morphology to papillomata that occur more commonly in the bladder and larynx. Their color, attachment, multiplicity, occasional tendency to recurrence, and microscopic appearance, as well as the general tendency to become malignant holds about equally for the papilloma appearing in these different regions.

Papillomata occurring in the rectum are lobulated or villous tumors varying in size from a pea-like nodule to a tumor the size of a child's head, as reported by Allingham. They usually have a sessile broad attachment on the mucosa which may be multiple with more or less normal appearing mucosa between the several points of attachment. These tumors rarely are pedunculated. They may have a surface of wavy villous prolongations that float in water. The surface of the tumor, on the other hand, may be coarsely

nodular as those that occur in the bladder and larynx, but still have a typical papillary structure microscopically. The tumor often has several lobes which in turn are divided into many small lobules (Figs. 8–11). The color of the papilloma is red and frequently clots of blood are seen adhering to the surface that has most recently bled. In consistency the tumor is characteristically soft and sponge-like and has no induration at its base or attachment. Multiple papillomata of the large bowel have been observed where the bleeding has been so great as to be serious. When this condition occurs above the reach of the examining finger the differentiation from a malignant growth is difficult to make.

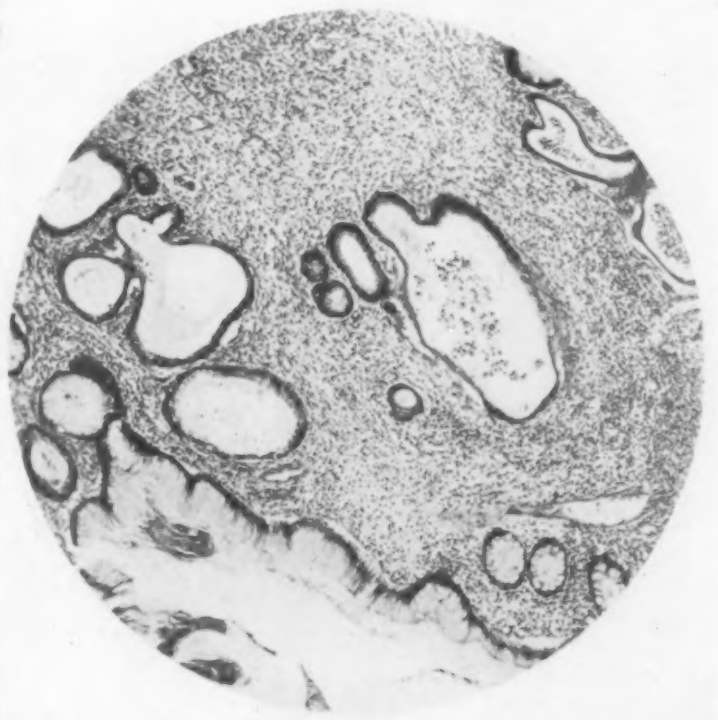

FIG. 2.—Simple pedunculated adenoma of the rectum, from male aged fifty years. Shows rich connective-tissue stroma containing gland acini, with varying degrees of cystic dilatation. At lowest portion of picture columnar epithelium covering the surface of the tumor.

Higher in the large bowel, papillomata are not commonly found. In the instance quoted as Case I, the tumor mass in the descending colon was so soft it could only be palpated with difficulty in the unopened bowel at the time of operation. It had a broad attachment to the mucosa and encircled the bowel with the exception of a small area opposite the mesenteric attachment. When the bowel was opened the tumor had a soft papillary structure without induration with a raised margin, which made a definite line of demarcation from the normal mucosa of the bowel. There was no ulceration over the tumor mass. Sections of this tumor are seen in Figs. 5, 6 and 7.

The tendency to recurrence after removal of papillomata of the large bowel does not seem as great as in bladder or laryngeal papilloma. It may be that the thoroughness of removal of the tumor mass can be better guaranteed in the rectum. On the other hand, several instances have been recorded

where recurrence has taken place several times after operative removal of papilloma of the rectum. Recurrence of the tumor in other locations in the bowel is also possible. In Case II several small papillomata appeared on the mucosa of the colostomized bowel where the colostomy was done to decrease the bleeding in a nearly exsanguinated patient who had multiple papillomata in the ampulla of the rectum. The structure of these new tumors is shown in Fig. 12.

The microscopic appearance of these papillomata of the large bowel varies in some degree, dependent on their attachment to the mucosa of the bowel. In the pedunculated papillomata there is found a marked connective-tissue framework containing blood-vessels, fibroblasts, some muscle cells, wandering cells of different types and round-cell accumulations of varying degree. In this connective-tissue pedicle no granulation tissue is seen. The connective-tissue stroma branches and rebranches to the finest ramification of the papillary outgrowths at the periphery of the tumor. Near the base of attachment the epithelium takes on a more or less glandular appearance with acinus formation. Some of the glands are dilated, the epithelium is low, and small nuclei are present in the base of the cells. Cyst formation is occasionally seen (Figs. 9 and 10, Case V). Farther to the periphery of the tumor the epithelium takes on a different character in that the cells are columnar with rather clear protoplasm with elongated basal nuclei. There are usually many goblet cells to be seen. In the papillary projections of the tumor the epithelium is higher, the nuclei are usually multiple, are inclined to be hyper-

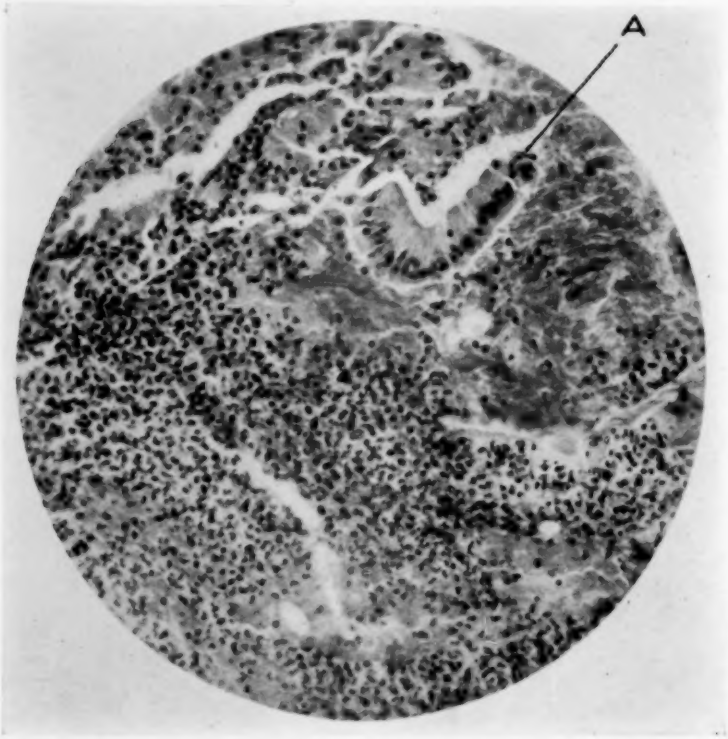

FIG. 3.—Pedunculated adenoma of the rectum with marked inflammatory exudate, from a child aged three years. Only epithelial element found in many sections shown at A.

chromatic and mitoses are not infrequently seen. The basement membrane, however, is everywhere intact, and except at the periphery of the tumor, the muscularis mucosa is easily seen and is intact.

In the more common type of papillomata where the attachment is sessile, the papillary structure of the tumor seems to spring from the mucosa of the bowel and the papillary projections take the place of the normal mucosa. Here and there, miniature connective-tissue pedicles run into the mass, making a fine reticular stroma containing blood-vessels, fibroblasts, and wandering cells. The adenomatous feature of the mucosa is more in the background, but the character of the epithelium covering the papillary projections correspond to the description given for the pedunculated type.

The relation of adenomata of the bowel to papillomata seems to be very close. Not only are simple adenomatous structures found in most papillomata, but characteristic cystic degeneration of the adenomatous structure is also observed (Fig. 10). Some tumors have been observed where certain portions are wholly adenomatous and other portions of the same tumor take a papillomatous structure (Fig. 13). Grossly, adenoma which are usually pedunculated (Fig. 1) may have a smooth surface or may be finely lobulated like papilloma, in which event it is difficult to foretell the exact microscopic picture. Inflammatory polyps having the appearance of pedunculated adenoma may arise from the chronic ulcerative processes in the large bowel, which microscopically have no epithelial covering and consist of granulation tissue and fibroblasts along with a rich cellular exudate. Pedunculated adenoma are observed where microscopically the adenomatous structure is almost entirely lost and in which the products of inflammation are the predominant picture (Fig. 3). These varying clinical and microscopic pictures suggest very strongly the possible influence of inflammation in the formation of this class of tumors in the large bowel. In this connection it should be stated that Doctors Belleli [5] and Milton [6] have reported finding Bilharzia Hæmatobia in adenomata of the rectum. Ball cites a case where the ova of the oxyuris vermicularis were found in the substance of a papillomatous tumor of the bowel.

Relation of Papillomata of the Large Bowel to Carcinoma.—The consideration of these tumors as potentially malignant or as pre-cancerous growths offers a chance for considerable speculation.

Quenu and Landel, who wrote the first important monograph on these tumors, state that they are all types of " épithéliome cylindriques " and correspond to the slowly growing epithelioma of the face in old people. They base their contention on the fact that at the periphery of the papillary structures the cells have multiple, hyperchromatic, deeply staining nuclei with few goblet cells and correspond to the cells seen in papillary cancer of the rectum.

Goebel states that the malignancy does not take place in the periphery of the tumor but at the base, and describes very carefully two cases which had the appearance of benign papillomata of the rectum, but which on

microscopic examination revealed the basement membrane broken and penetrated by epithelial elements invading the submucosa in one small portion of the tumor. He collected 57 cases from the literature up to 1914, of which he believes 8 were malignant, including both of his own. He states all papillomata of the large bowel should be regarded with suspicion as to their malignancy.

Mummary, in his text-book of 1923, reported one case of papillomata of the rectum and sigmoid and states that all adenomata of the large bowel eventually take on a malignant change (Fig. 14).

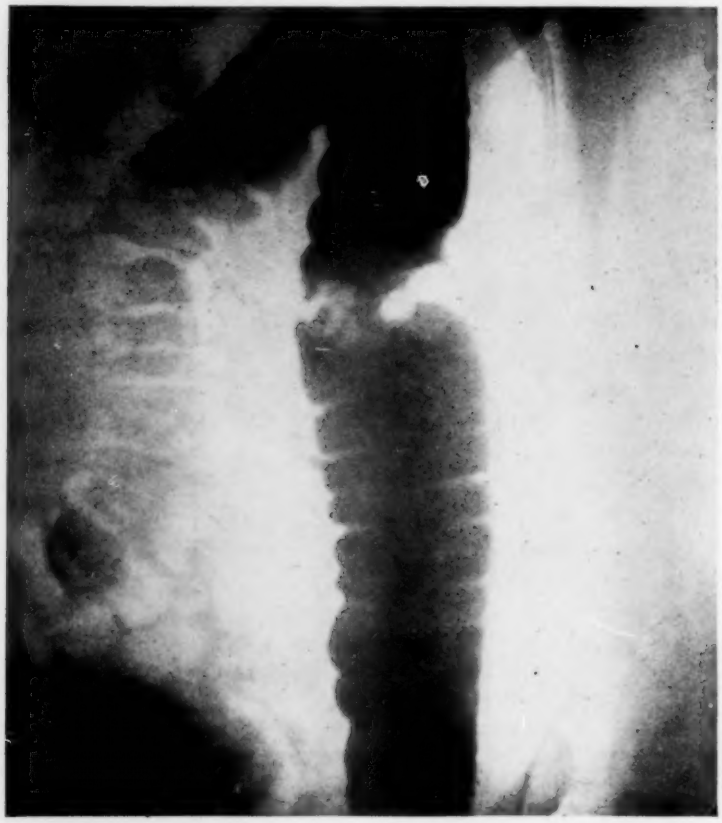

FIG. 4.—Case I. Filling defect due to papilloma of descending colon.

Practically all writers on this subject regard papillomata of the large bowel with more or less suspicion as to their pre-cancerous nature. Some regard every such tumor as one which if not malignant at the time of examination will eventually become so. Others simply speak of these tumors as potentially malignant.

It has been possible for us to study nine tumors of the large bowel which we believe should be classified as papillomata or adeno-papillomata. Eight of these patients were examined by us or were under our care, so that a history of the lesion, numerous clinical examinations of the tumor *in situ*, as well as the material for histological study, were available for diagnostic purposes. Histological study alone was possible in one additional tumor of this type. Appended to the article are the histories and results of histological examination of the tumors, as well as the treatment employed. The question of the malignancy or pre-cancerous nature of these tumors was constantly in mind.

While deeply staining hyper-chromatic nuclei undergoing occasional mitosis are findings in a benign tumor that are suspicious of malignancy, they are changes not uncommonly found in rapidly growing epithelial tumors. While such microscopic changes are not to be neglected in weighing the evidence as to the malignancy of the tumor, it seems of much greater importance to observe the regular arrangement and form of the epithelial cells on the basement membrane which everywhere presents an unbroken continuity in a benign tumor. In other words, the infiltrative character of the tumor is of the greatest significance in the microscopic study of a malignant tumor (Figs. 14–17). Coupled with this, and of almost equal importance, is the gross pathological appearance and "feel" of the tumor as well as the clinical history of its growth. These are the criteria we have used in the diagnosis of the benignancy or malignancy of the tumor. Small pieces of these tumors are not sufficient in themselves to allow proper histological study to be made, but sections must be studied which run through the base of the tumor and its attachments.

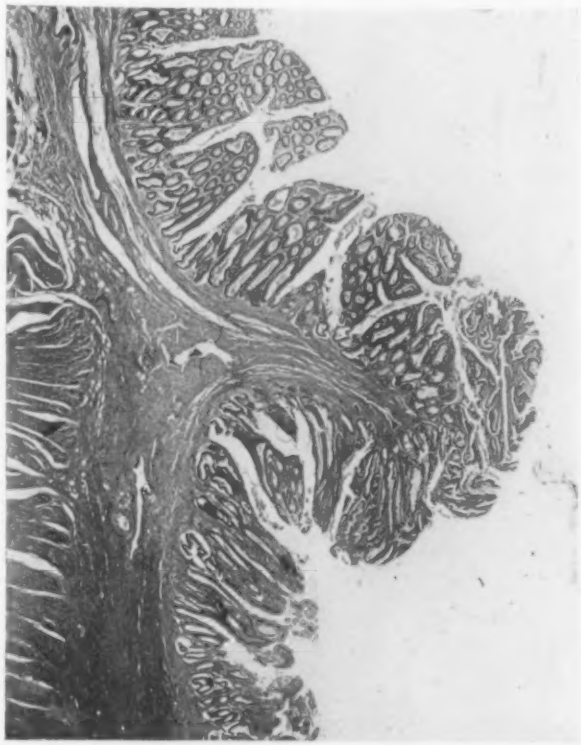

FIG. 5.—Case I. Twelve diameter magnification of section from papilloma of descending colon, shows tumor taking place of normal mucosa. In one area, delicate pedicle formation.

In considering our cases the clinical suspicion of malignancy was always enhanced where the tumor was high in the rectum or large bowel, and was therefore not accessible to palpation or to the helpful "feel" of the tumor mass. In this type of tumor the lesion was usually of longer standing. The anæmia of the patient was more marked and the filling defect on fluoroscopy made the diagnosis of carcinoma most probable. In Cases I and II, the above findings were all present and the presumptive diagnosis of malignancy was made. In Case I, where the filling defect (Fig. 4) was just below the splenic flexure, it was barely possible to feel a difference in consistency in that portion of the bowel occupied by the tumor as compared to portions of the bowel above and below it. The tumor-bearing portion of the bowel was resected in this patient by a three-stage Mikulicz procedure and a papilloma nearly

encircling the bowel attached by a broad base on the side of the mesenteric attachment was found. Many sections of this tumor (Figs. 5, 6 and 7) show its benign character. The tumor is formed by elongation of the mucous membrane into papillary structures, although a slight degree of adenomatous changes are found in some areas (Fig. 5).

With some minor variations the history and findings in one other tumor in this location presented the same picture and no evidence of malignancy was found (Case II).

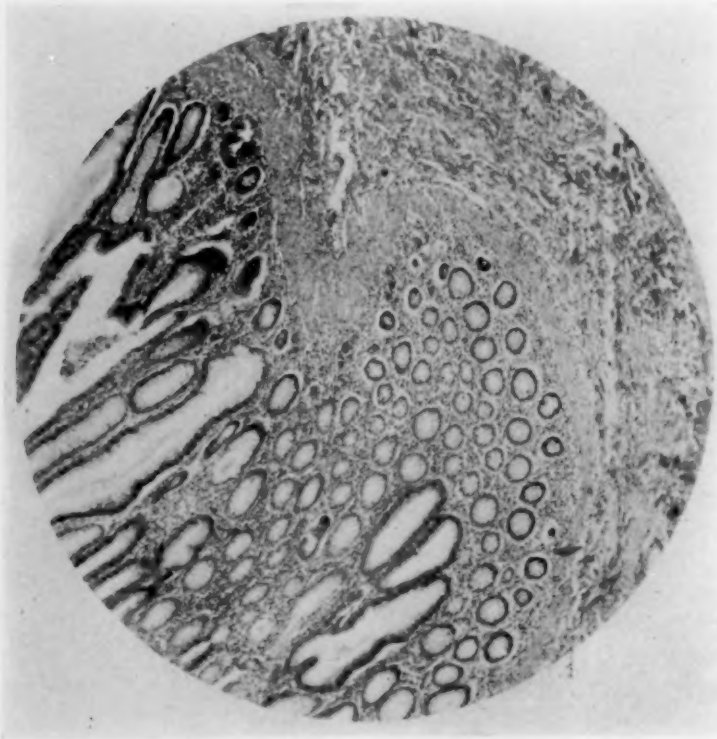

FIG. 6.—Case I. Magnification sixty diameters, shows small area of adenomatous acini next to base of papillary projections. Intact muscularis mucosa.

Another patient (Case III), with a tumor in the ampulla of the rectum which had a broad attachment and no evidence of deep fixation of tumor to bowel wall, presents clinical history and appearance of a benign papilloma and it is being treated as such.

Five patients had papillomata of the rectum which were within reach of the examining finger and which, with one exception, protruded at bowel movement. It was therefore easy in this group to determine the physical characteristics of the tumor. In all but one, the tumor was soft and spongy; was not ulcerated, and had a point of attachment on the mucosa which presented no evidence of induration or fixation to underlying structures (Fig. 11). Only one of these tumors was pedunculated (Fig. 8). In these patients the microscopic picture bore out the clinical impression of the benign character of the tumor. The basement membrane was everywhere preserved and while hyper-chromatic and mitotic nuclei were occasionally seen, there was no infiltrative characteristics of carcinoma (Figs. 9 and 10). The exception to this statement presented a very interesting problem (Case VII). A woman sixty-three, who had been operated upon for bleeding hemorrhoids two

years previous to the present observation, had been bleeding from the rectum for six months and had suffered some sharp sticking pain in the rectum. Biopsy had been performed on the tumor mass situated just above the mucocutaneous line, which showed a benign papilloma microscopically. This tumor nearly encircled the rectum and was soft and villous in character, except in one area about the size of a 50-cent piece, where there was induration and fixation of the tumor but no ulceration (Fig. 15). A biopsy of the tumor at this point of induration showed a carcinoma infiltrating the submucosa (Fig. 17). Due to the anæmia, weakness, and age of the patient, a posterior resection of the rectum was performed, removing the bowel well above the tumor mass, including the fat and levator muscles surrounding the bowel. Sections including the whole thickness of the bowel over the soft papillomatous area of the tumor showed, in most places, a benign papillomatous structure without invasion of the basement membrane (Fig. 16). In many sections examined of the soft papillomatous portion of the tumor, the cells presented hyper-chromatic and occasionally dividing nuclei, but there was no invasion of the basement membrane. Whether the tumor was malignant from the start, with papillomatous overgrowth on the surface of the surrounding bowel, as I believe it was, or whether it represents the early malignant degeneration of a papilloma is not easy to decide. The clinical appearance and "feel" of this tumor made the probable diagnosis of carcinoma reasonable, and before the biopsy of the indurated area I felt no hesitancy in saying that a radical removal of the bowel in which this tumor mass rested, was advisable.

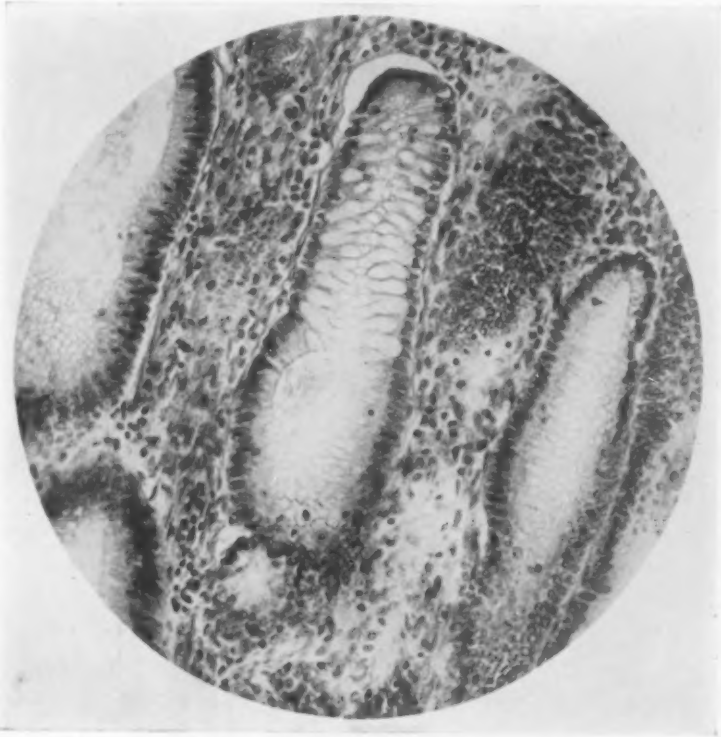

FIG. 7.—Case I. Magnification 230 diameters, shows character of columnar epithelium and connective-tissue stroma in the papillary portion of the tumor.

The remaining instance of papilloma of the bowel is questionable in that an examination of the patient, the only child in this series of patients, was not possible. Several large fragments of tumor material, regular in outline, but with a finely lobular surface, were the only evidence available for examination. The tumor masses had been passed spontaneously. The examination of this tumor microscopically (Fig. 13), showed both adenomatous and papillomatous areas, which were benign in appearance as far as the specimens examined allowed one to say.

To summarize, we believe that where adequate clinical and microscopic examination of a papillary tumor of the large bowel is not possible to obtain, they should be radically removed, resecting, if necessary, the bowel in which the tumor is situated. If there are evidences of induration to palpation or microscopic evidence of breaking through basement membrane, tumor should be regarded as a carcinoma and radically treated as such. If, on the other hand, clinical evidence shows a soft, non-indurated tumor, fair presumption is that tumor is benign and should be treated by local removal. Microscopic examination is important, but should be weighed with the clinical examination of tumor.

FIG. 8.—Case V. Gross appearance of pedunculated villous tumor of rectum.

Treatment.—The treatment of papillomata, which are regarded with suspicion as to their malignancy, should involve the same surgical principles used in treatment for carcinoma of the large bowel, namely, wide removal of the bowel in which the tumor lies, including the lymphatics which drain that portion of the bowel.

In the benign papillomata of the lower rectum the tumor may be prolapsed through the anus, the healthy mucosa around the base of the tumor picked up by Allis forceps and an excision of the tumor carried out through healthy mucosa and submucosa. The defect in the mucosa made by such removal of the tumor may be partially closed by suture or allowed to granulate.

When benign papillomata lie above the point where they may be prolapsed through the anus the problem is harder. We have elected to treat such tumors by fulguration or actual cauterization through the proctoscope. This requires some special instrumentation and several sessions of treatment, but can be successfully done with a thorough cauterization of the base of attach-

ment of the tumor. One of the cases reported (Case III) is of this nature. We have not reported several other tumors which in appearance corresponded to papillomata by reason of their lobular, easily bleeding surface because no adequate microscopic examination was possible. Treatment by fulguration and cauterization adds the element of acute inflammation to tumor growth, which has some theoretical disadvantages. The alternative, however, of making a posterior approach to the ampulla of the rectum and opening the bowel into what has every appearance of a benign tumor, does not appeal to me, even though adequate microscopic examination is lacking.

CONCLUSIONS

(1) Benign papillomatous tumors of the large bowel are probably more common than the literature would indicate.

(2) There is a close relationship between adenoma and papilloma of the large bowel. Most papillomata have adenomatous constituents, some of which may be cystic.

(3) The relation of the origin of these benign epithelial tumors to inflammation is suggested.

(4) Papillomata of the large bowel should be regarded as pre-cancerous lesions and removed or destroyed.

(5) The diagnosis of malignant changes in papillomata of the large bowel should be made by clinical appearance and "feel" of the tumor, as well as by the infiltrative characteristics of the tumor microscopically.

(6) Probably less than 25 per cent. of papillomata of the large bowel are malignant at the time of their observation.

REPORT OF CASES

Papillomata high in the rectum at the recto-sigmoidal junction or descending colon.

Case I.—Mrs. M. L. Entered Presbyterian Hospital, February 10, 1924, age fifty-seven. Referred by Doctor Allin.

Present complaint: For the past three weeks the patient has had a bloody diarrhœa, at which time she has had abdominal distress and cramps, and marked urgency to go to stool. At each bowel movement a few tablespoonsful of bright red blood were passed and occasionally dark clotted blood would be expelled. During the day there was desire to go to stool about every fifteen minutes, but at night time the urgency was much less. The present attack began in January, 1924, but lately the bleeding has become much more profuse, and three days ago there was a severe hemorrhage during which time over a pint of blood was lost. The blood at this time was bright red and free from clots.

Past history: The patient has had four similar attacks of hemorrhage within the last two years coming about six months apart and lasting three to six weeks at a time, each attack having the same symptoms, and in the period of remission microscopic blood being absent from the stools. During this period she has become increasingly constipated and has found it necessary to move her bowels by frequent catharsis. She is unable to say whether diarrhœa would be present if she did not take cathartics. When formed stools have been passed they have been of small calibre. General abdominal tenderness has been present during this period. At the time of bowel movements there has been no protrusion from the rectum and no pain in the rectum. The general

history of disability in respiratory, cardio-vascular, or genito-urinary tracts is absent. There have been no ulcer symptoms. She has lost no weight.

Physical examination reveals a well-nourished, well-developed woman, not acutely ill. Slight pallor of the conjunctiva and buccal mucosa but no suggestion of jaundice. Regional examination is negative, except in abdomen where there is a generalized tenderness, especially along the descending colon. There is a spot of marked tenderness midway between iliac crest and costal margin on the left side. Rectal examination: There is a small fibrous polyp at the mucocutaneous line but otherwise digital examination is negative and proctoscopic examination of the recto-sigmoidal junction reveals a normal bowel. Vaginal examination is negative.

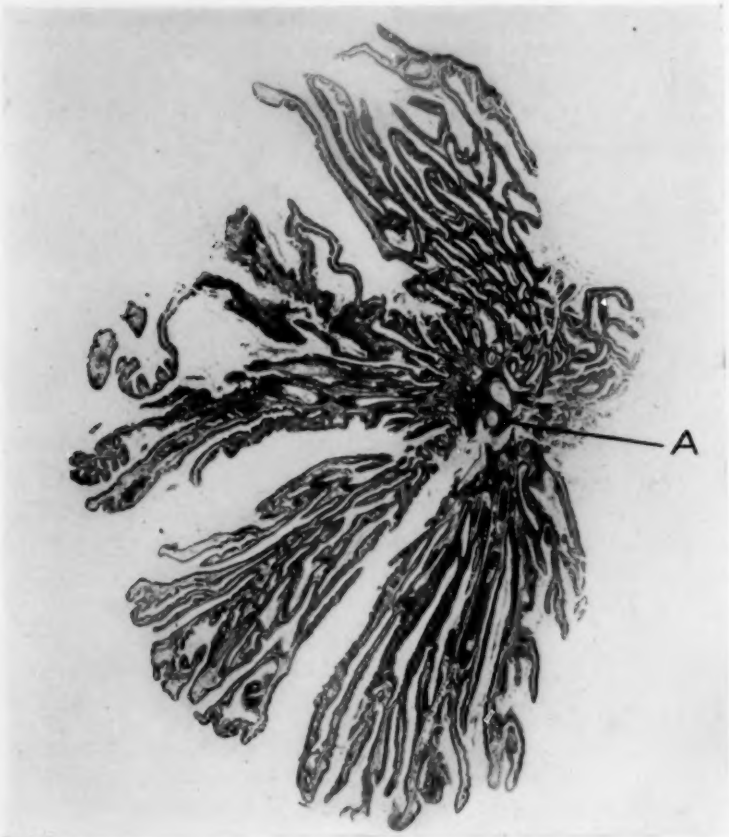

FIG. 9.—Case V. Magnification seven diameters of a section showing exquisite papillary arrangement of the tumor. At A are shown some dilated acinous structures resembling those found in pure adenoma.

Fluoroscopy of the colon, February 12, 1924: Barium entered readily, filling the colon easily as high as the upper end of the descending portion. Here there was a definite irregularity consisting of a considerable constriction of the lumen for a distance of perhaps an inch. This finding remained constant throughout the entire examination. Immediately above and below this point there was an excellent filling of the colon and elsewhere the colon was well filled. Films depict the findings noted on fluoroscopic examination (Fig. 4), and show an irregular super-imposable filling defect just below the splenic flexure.

Films taken later show no definite retention in the colon above this defect.

Reëxamination February 14 shows the same defect in the same position and of the same type as on previous examination. Findings are compatible with the filling defect from carcinoma.

Stool examination made on numerous occasions showed blood but very little mucus and no pus. Diagnosis was probable carcinoma of the descending colon, although a benign neoplasm was considered possible due to the history extending over two years,

the absence of cachexia, the absence of obstruction of the bowel, and the absence of pus in the bowel movement.

Operation February 16, 1924: Ether anæsthesia. Left rectus incision. Descending colon, from splenic flexure to sigmoid, palpated. No tumor mass was made out. Feeling sure that the persistent filling defect in X-ray was not due to spasm, the splenic flexure and descending colon was mobilized by division of the lateral peritoneal attachments and the bowel was delivered into the wound, where it could be inspected and palpated more easily. About four inches below the splenic flexure a slight increase in the bulk of the intestine was felt as if some soft mass were present within the lumen of the bowel. This was not able to be milked downward or backward and was, therefore, regarded as the mass responsible for the filling defect. There was no change in the appearance of the bowel externally nor were there large mesenteric glands. The afferent and efferent loops of the bowel were sutured together opposite their mesenteric attachment by running catgut and the tumor-bearing area of bowel was anchored outside the peritoneum as first stage of a Mikulicz resection of the large bowel.

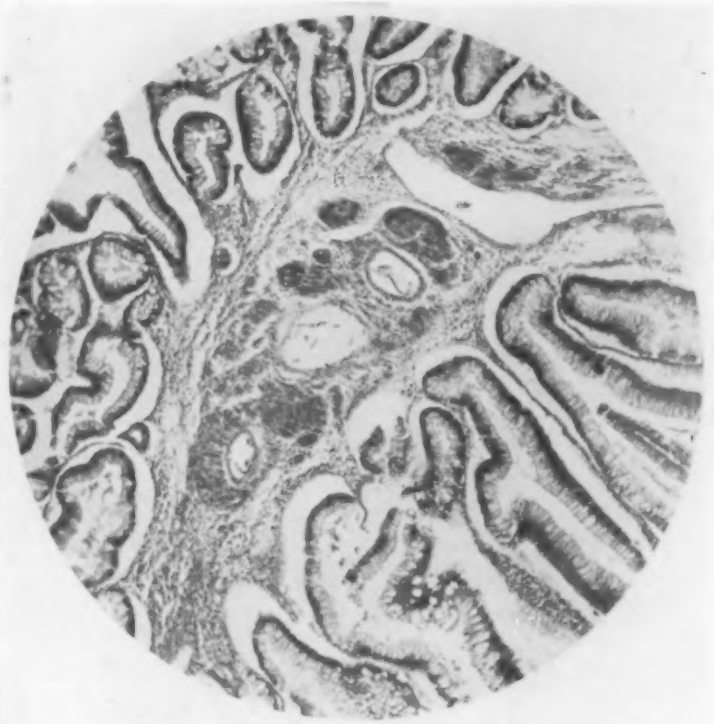

FIG. 10.—Case V. Magnification sixty diameters. In the centre of the section are seen cystic acini with flat epithelium. In the periphery of the section papillary projections with little stroma covered by columnar epithelium rich in goblet cells.

Second stage of the Mikulicz resection, February 18, 1924: Two days later the protruding loop of bowel was resected between intestinal clamps by cautery and the tube was inserted into the lumen of the upper segment. Bleeding mesenteric vessels were ligated.

Third state of the Mikulicz resection, April 6, 1924: A clamp was applied, dividing the spur between the two loops of bowel.

Examination of specimen: The resected portion of the colon was about 7 cm. long. A great deal of fat was present in the mesentery. The serous surface of the bowel was normal in appearance. The lymph-nodes remaining in the mesentery were apparently normal. On the mucosal surface of the bowel there was a verrucous or villous tumor about 5 cm. long and 3 cm. wide which nearly encircled the bowel, except at a point opposite the mesenteric attachment. It had a broad sessile base of attachment. The tumor had elevated edges though there was no induration at the point of attachment to

the large bowel. The consistency was soft and spongy but somewhat more firm than the surrounding normal mucosa. It is easily movable and did not seem to involve the muscular or serous coats. There were two remaining areas of tumor growth very near to the tumor just described, but which had separate points of attachment to the mucosa of the bowel. The color of the growth was red.

Microscopic examination of the tissue from several different portions of the tumor, including the complete thickness of the bowel wall, revealed a benign papilloma (Figs. 5, 6 and 7). The epithelium was greatly elongated into papillary extensions, in each of which was a connective-tissue stroma containing capillaries, fibroblasts, and wandering cells. The connective-tissue stroma in some places formed a miniature pedicle which extended into the epithelial mass of the tumor. At the base of these small pedicles were round-cell accumulations and in several places areas of adenomatous tissue with acinous formation. The cells lining the acini were low with small nuclei at the base of the cells. Hyperchromatic or mitotic nuclei were not seen. The epithelium covering the delicate papillary projections of high columnar cells in which were seen numerous goblet cells. The nuclei were elongated, deeply staining, and situated at the base of the cells. In many areas the cells contained two or three nuclei of regular elongated shape. The basement membrane was everywhere intact and the muscularis mucosa was well defined and intact except in the fine papillary projections of the tumor. The submucosa and muscularis under the tumor was unchanged and not to be distinguished from normal bowel wall. Microscopic sections of the mesenteric glands showed no pathological changes.

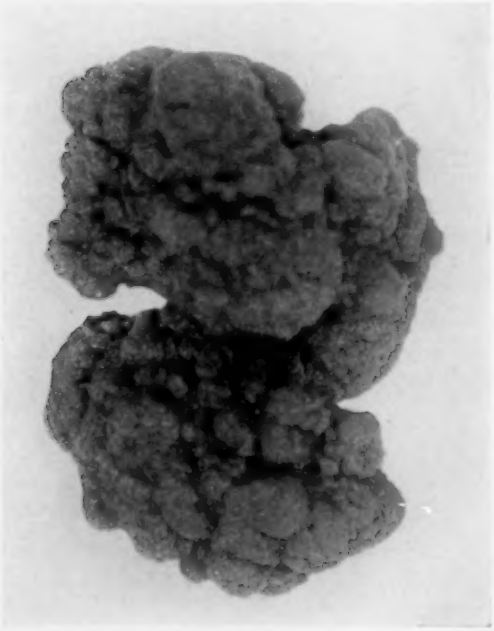

FIG. 11.—Case IV. Gross specimen of papilloma of the rectum.

The diagnosis was benign papilloma of the descending colon.

April, 1925: The patient is well. Has no complaints. The fecal fistula has been closed for ten months.

CASE II.—N. E., male, age thirty-eight. Entered Cook County Hospital, April 7, 1924, complaining of bleeding of bright red blood from the rectum, weakness, shortness of breath, and inability to work.

Past History: The bleeding has been present for one and one-half years and was thought to be due to hemorrhoids, which were removed nine months ago with only temporary relief. He has lost no weight. His color has been very anæmic, his skin and mucosa being almost transparent. He has been constipated and has some tenesmus at stool. He has had no pain. Denies venereal diseases. Wife has two children living and well. No miscarriages.

Examination revealed a well-nourished but very anæmic patient. General physical examination was negative except for a barely palpable spleen. Urine negative. Blood Wassermann negative. Blood: Hæmoglobin 28 per cent., red blood-cells 3,000,000. Stool examination negative except for blood. Fluoroscopy of colon was negative for pathological changes. Digital rectal examination was negative except for bright blood on the examining finger.

A proctoscopic examination, including the region 22 cm. from the anus, revealed at a point 12 cm. from the anus a bleeding surface which after application of adrenalin could be seen to consist of several finely lobulated papillary structures about 1½ cm. in height with a sessile attachment to the mucosa. These appeared to snap into view over the end of the proctoscope which led us to believe that they had a slightly indurated consistency. The area of the bowel involved was about 2 to 4 cm. long. A probable diagnosis of carcinoma of the rectum was made and colostomy was advised.

At exploratory operation, the rectum at the peritoneal reflection was soft and unchanged in external characteristics, but an indefinite small mass was thought to be felt in the bowel. There was no glandular involvement. The picture from the abdominal side was not that of carcinoma or diverticulitis. A colostomy without dividing the bowel was done.

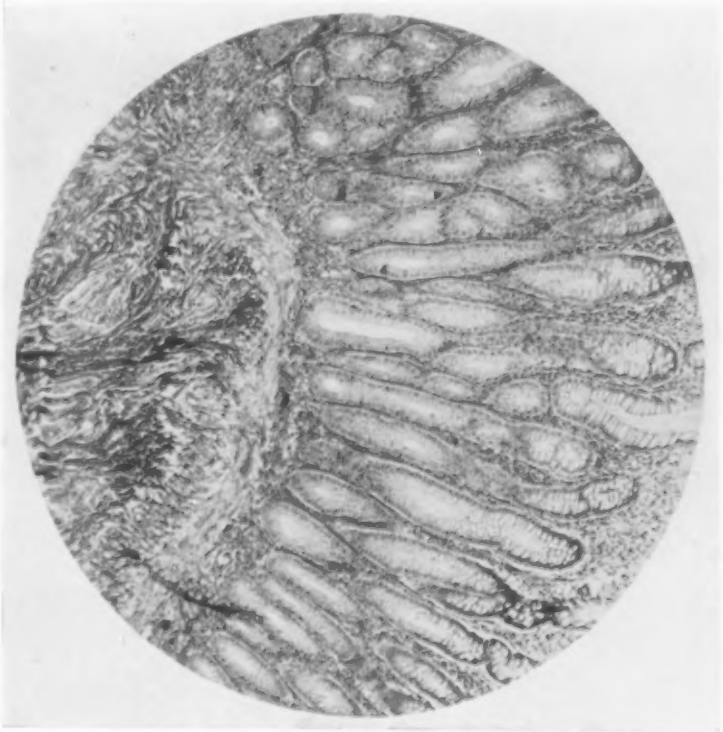

FIG. 12.—Case II. Magnification sixty diameters of small papillomatous tumor occurring on mucosa of colostomized bowel, showing intact muscularis mucosa, round-cell infiltration in connective-tissue base, and branching papillary projections, covered with columnar epithelium rich in goblet cells.

Following the operation 1/10 per cent. silver nitrate five-minute retention enemas were given daily per rectum. The hemorrhage ceased and the welfare of the patient improved in every way. His blood picture gradually returned to normal and he urged that his colostomy be closed.

Repeated proctoscopic examinations during the succeeding ten months showed a bleeding surface but a gradual recession of the papillary tumors, until finally no tumor was visible and the surface of the bowel was practically normal. We have no explanation to make for this phenomenon. Still feeling that a carcinoma might be present where these papillomata were, pieces of tissue were removed from the bowel wall through the proctoscope, but no tumor tissue was seen. In the beginning of 1925, several elevated papillary masses with sessile attachment of about ½ cm. in diameter appeared on the mucosa of the colostomized bowel. These were excised and a microscopic study of them shows an elevated epithelial covering with papillary elongations, the epithelial cells of which are columnar, with well-stained basal nuclei. The basement membrane is intact (Fig. 12). There is no particuar evidence of round-cell or polymorphonuclear exudate at the base of, or in the tumor itself. It appears that the mucosa of the colostomized bowel was involved by the same type of papillary epithelial tumor growth that affected

the ampulla of the rectum. After excision of these tumors they did not recur in the few weeks that the bowel was open to inspection.

Yielding to the constant plea of the patient that the colostomy be closed, this was done in the latter part of March, 1925. What the future of this paient will be is problematical. It seems to me proper, however, to include this unusual case in the list of papillomata of the large bowel.

Papillomata in the ampulla and lower rectum.

CASE III.—R. McC., male, age forty-eight. Entered Presbyterian Hospital, March 7, 1925. Referred by Doctor Stevens, complaining of blood in stools and distress in lower abdomen.

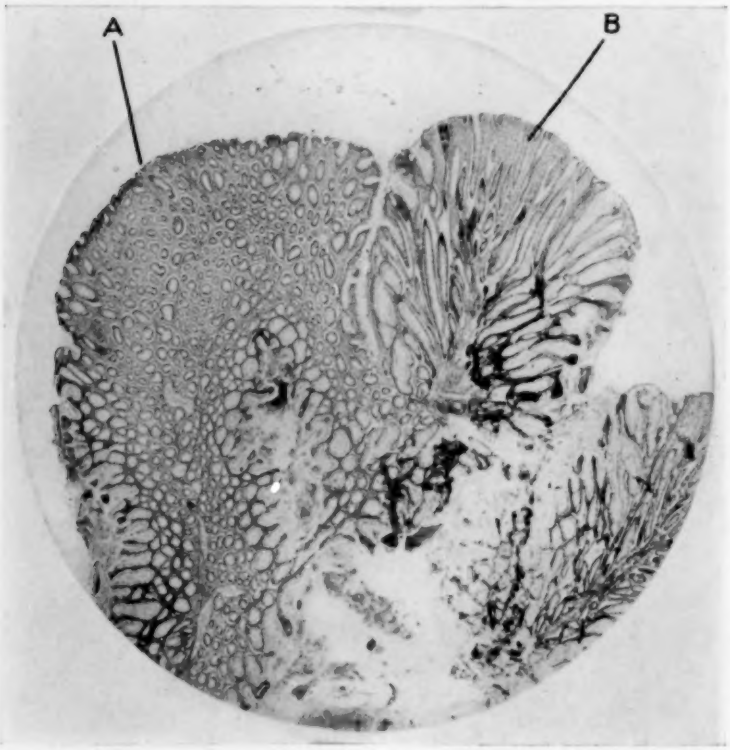

FIG. 13. Case IX. Magnification twelve diameters of a section of tumor fragment, showing A, adenomatous structure; B, papillomatous structure.

Patient states that about two months ago he began to have an uncomfortable feeling in his lower abdomen, just below the navel in the midline. The distress is more like a burning sensation than a pain. The distress is not affected by eating or by bowel movements.

About three weeks ago, the patient noticed considerable blood in his stool. The blood was very dark. The patient states he has not noted it in his stools since. From the time he noted this blood his stools have been rather mushy in character and brown in color. He states he has no distress on bowel movements. His general health is good. He has lost no weight.

A general examination of the patient was essentially negative as far as pathological processes were concerned, with the exception of the proctoscopic examination. Twelve centimetres from the anus a finely lobulated bright red tumor mass, consisting of several coarse lobes, was attached by a broad base to the right anterior aspect of the ampulla of the rectum. Part of the attachment was on a prominent valve of Huston, and the remainder of the attachment ran behind the valve and required considerable air dilatation to reveal it. The tumor was about the size of an English walnut and was partially hidden by the prominent valve mentioned. It was freely movable and could be prolapsed for an inch when grasped by a fine forceps. The surface was not ulcerated and there was no evidence of indurated fixation of the tumor to the bowel wall.

The appearance of the tumor and the clinical history was that of a benign papilloma.

A biopsy of the tumor had been performed before the patient entered the hospital. An examination of these sections, which did not include the attachment of the tumor to the bowel, showed typical papillary projections, with a fine stroma of connective tissue containing thin-walled blood-vessels, wandering cells and occasional round cells. The epithelium covering the papillary stalks was columnar, with well staining, often multiple long nuclei. Mitoses were rare. Goblet cells were rather numerous. While the microscopic examination of the tissue was not conclusive because only a small portion of the tumor was examined, the clinical history and physical characteristics of the tumor indicated its benignancy.

Treatment.—Fulguration of the tumor in several sessions was elected as the most conservative treatment, as the tumor had every appearance of being benign. This treatment is now being carried out.

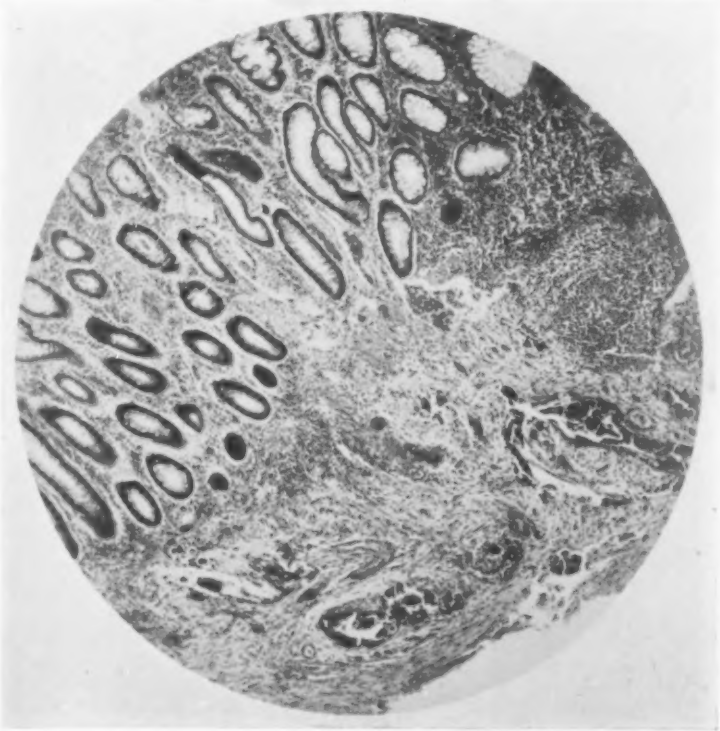

FIG. 14.—Early malignant degeneration of simple adenoma of the rectum, showing infiltrative characteristics with penetration of basement membrane.

CASE IV.—Mrs. F. M. age forty-three. Referred by Dr. R. C. Brown. Patient has had marked bleeding from the rectum associated with protrusion of a soft mass at bowel movement for several years. She had always thought she had hemorrhoids. There were no general symptoms or complaints except constipation. The general examination of the patient was essentially negative. Rectal examination revealed a soft, easily bleeding tumor mass about the size of a hen's egg, red in color, with a coarse lobular contour and a finely lobulated surface. It was attached by a broad base about one inch in diameter to the right anterior portion of the rectal mucosa just above the mucocutaneous line. There was no induration at the base of attachment (Fig. 11—Gross specimen).

Under ½ per cent. novocain anæsthesia the tumor was removed by cautery, removing normal mucosa and sub-mucosa around the tumor.

The microscopic examination of tissue from several portions of the tumor, including the base of attachment, confirmed the clinical diagnosis. In several places there were small connective-tissue projections into the tumor mass which contained thin-walled blood-vessels and wandering cells. There were also widespread accumulations of round cells. This round-cell accumulation was very marked in some places in the tumor and

could be regarded as a chronic inflammatory change. The epithelial covering of the tumor consisted of columnar cells which contained elongated nuclei. Most of the nuclei were stained deeply but in some areas of the tumor the nuclei were vacuolated. There were occasional goblet cells scattered throughout the epithelium. The basement membrane was everywhere intact and there were no infiltrative changes in the tumor grossly or microscopically.

At the point of attachment of the tumor to the bowel wall there were some adenomatous structures consisting of acini lined with columnar epithelium and having the appearance of the acinous structures found in adenoma of the bowel. These structures were, however, only occasional and did not predominate in any of the sections studied. The diagnosis was adenopapilloma of the rectum.

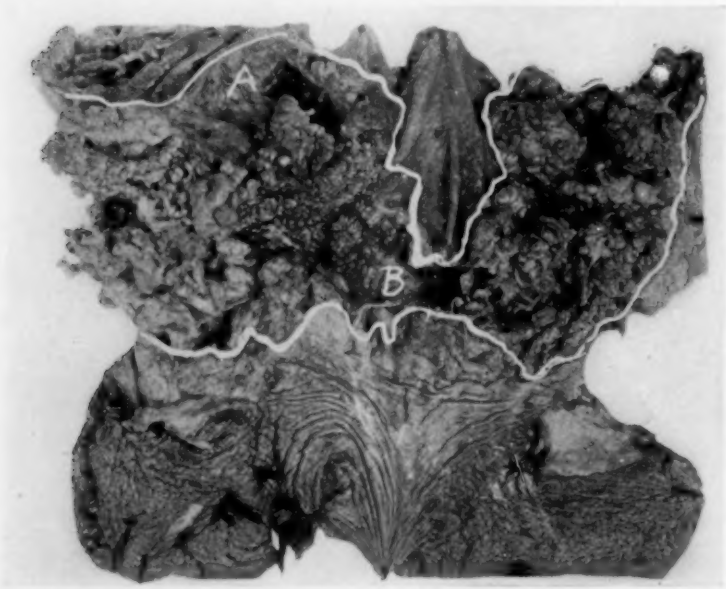

FIG. 15.—Case VII. Gross specimen of tumor of the rectum, showing soft papillary non-indurated tumor at A, and a small area of carcinomatous indurated tissue at B.

CASE V.—R. T., male, age fifty-five. Dr. D. W. Graham's patient. Entered Presbyterian Hospital, February 24, 1920, complaining of a protruding mass from the rectum; bleeding from rectum; pain in lumbar region.

Rectal complaint has been present one year. A mass which has constantly grown larger has prolapsed at each bowel movement. The mass has bled freely each time and there is practically always blood on the stools.

He has lost about 85 pounds in weight in one year.

Operation, February 15, 1920: The sphincter ani was dilated with the fingers. A villous mass, about the size of a lemon, and attached by a pedicle to the right posterior wall of the anal canal, was delivered. The pedicle was transfixed and the tumor cut away.

Grossly the tumor mass was soft and spongy, red in color, with no areas of induration. The many papillary projections were striking because of the delicacy of their structure and unusual length. The appearance justified the name of "villous tumor." The point of attachment to the mucosa was a pedicle about 1 cm. in diameter which appeared to be covered with normal mucosa of the bowel. Figure 8 shows the size and shape of the tumor, but as the picture was taken five years after the removal of the tumor, the finer details of structure are lost. Figure 9 shows the gross villous character of the tumor.

Microscopically, the connective-tissue stroma was very marked at the point of attachment of the tumor and this broke up into numerous branches re-dividing many times to form a framework for even the finest papillary projections. There were present gland-like structures in the connective-tissue stroma lined with low columnar or flat epithelium. The acini varied in size and in the height of the columnar cells lining them.

Some were considerably dilated and cystic as are so commonly found in pure adenoma of the large bowel (Fig. 10).

The columnar epithelium covering the papillary projections corresponds in character to that described for the preceding specimens. There were a few isolated accumulations of round cells in the tumor. Nowhere was there a tendency for the tumor to infiltrate. Diagnosis: Benign pedunculated villous tumor.

The later history of this patient is not available.

CASE VI.—W. Y., male, age fifty. Entered Presbyterian Hospital, June 14, 1920, complaining of bleeding from rectum; protrusion from rectum; irritation of rectum.

Patient states he has had some rectal trouble all his life. His mother told him he had a hemorrhoid at the time of his birth. This has not annoyed him to any marked degree until about six years ago, when he noticed a protrusion from the rectum. There had been some bleeding at various intervals, mostly at the time of bowel movement. The "polypus" has been getting larger and of late has annoyed him considerably.

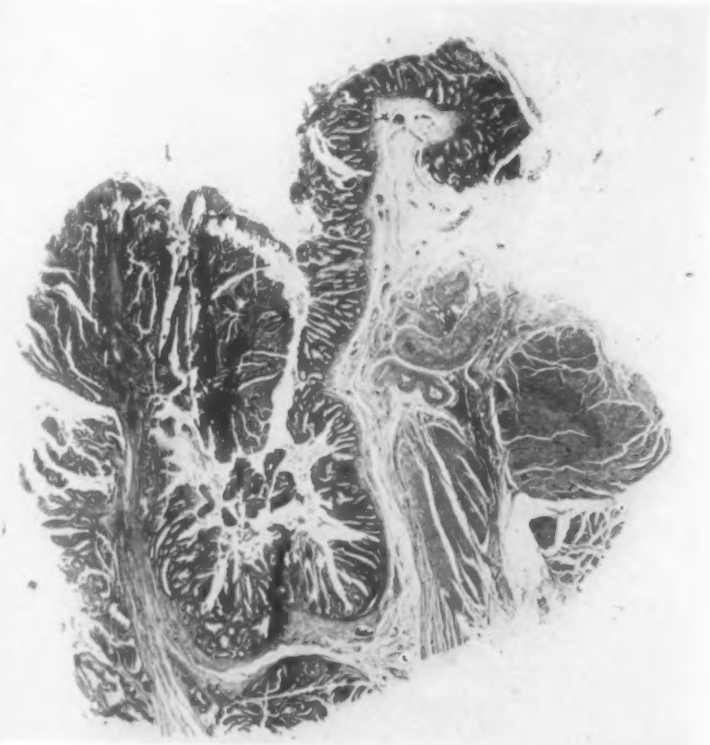

FIG. 16.—Case VII. Magnification eight diameters of section through junction of papillomatous tissue and normal mucosa. (A on Fig. 14), shows papillary character of the tumor with absence of infiltration.

Rectal examination revealed a red lobulated tumor mass about one inch in diameter, attached by a sessile base to the right anterior quadrant of the lower rectum. There were also internal hemorrhoids in other quadrants of the rectum covered with smooth mucosa. The papillomatous tumor, as well as the hemorrhoids, were removed by cautery.

Grossly this tumor was about the size of a hickory nut with a flat sessile attachment to the mucosa. The color was red, the consistency was soft and spongy. The surface of the tumor was made up of several coarse lobules which, in turn, were finely lobulated. There were no indurated areas in the tumor.

Microscopic examination showed the tumor taking the place of the normal mucosa of the bowel without any special pedicle, although there were projections of connective tissue into the tumor at several different places. In the region of the muscularis mucosa there were numerous areas of round-cell infiltration. There was no marked vascularity of the tumor. In main, the tumor was adenomatous, consisting of varying sized acini,

some with marked cystic degeneration. In the periphery of the tumor there was a tendency for papillary elongations, some of which branched and re-branched. Here the epithelium was higher, the nuclei were more elongated and in several places mitotic figures were seen. There were very few goblet cells. There was no microscopic evidence of infiltration seen in this tumor. Diagnosis: Adeno-papilloma of the rectum.

Case VII.—Mrs. E. G., age sixty-three. Entered Presbyterian Hospital, September 17, 1924. Referred by Doctor Clark.

For the past six months the patient has noticed blood in her stools. This was not always present during that period, but she says she never went for more than a day or so without seeing blood. She thinks that when bleeding stopped her pain was more intense.

Fig. 17.—Case VII. Magnification sixty diameters of tissue taken from B, Fig. 14, shows infiltrative characteristics of the tumor. Adeno-carcinoma.

Pain is described as a pressing pain, like pins and needles, and is much worse when patient sits down. This has gradually grown worse during the last month and is now so marked that she remains standing when on the "L" or surface cars. She has lost considerable weight and feels weak.

While the patient always enjoyed good health, she has had a certain amount of urinary disturbance. For the last few years patient has had to urinate ten or twelve times daily and often sits on the toilet for an hour or two at night. Says she urinates often but passes only a few drops at a time. She was operated upon for hemorrhoids two years ago, at which time she had considerable bleeding in the stool. She was a pale, feeble old lady. Blood-pressure 170. Hæmoglobin 85 per cent.; red blood-cells 4,400,000; white blood-cells 6400. Pus in urine. Heart, lungs and abdominal examination negative. No œdema of extremities.

Rectal examination revealed a tumor mass, consisting of soft spongy tissue, almost fills the lower portion of the rectum. At one portion in an area about one inch in diameter, there is an indurated area in the mass which feels like a malignant tumor. By inspection, the tumor which is visible through a speculum is soft and wavy and has the typical appearance of a papilloma. There is no pus or old blood in the rectum.

Before the patient came to the hospital a biopsy on the tumor had been done which showed benign papilloma. Both Doctor Clark and I thought that the indurated character of one area in the tumor was very suggestive of malignancy. Another biopsy was

therefore done, taking some of the indurated area, as well as some of the soft spongy portion. The former showed an infiltrating carcinoma and the latter a benign papillary tumor without rupture of the basement membrane. The patient was advised to have a resection of the rectum from below because the tumor was low and her general condition was such that it was thought she could not stand a more radical combined operation.

Under ether the rectum, levator muscles and fat was excised well above the tumor mass by a Kraske posterior operation and the healthy bowel was drawn down and attached to the skin. She made a slow but uneventful recovery, has regained her normal weight, color, and at the present time has no evidence of recurrence.

The specimen consisting of the terminal six inches of the bowel, revealed when opened, a tumor mass beginning just above the muco-cutaneous line and involving the entire circumference of the bowel with the exception of a small area on the anterior wall. The mass extended upward about two inches and was in most places red, soft and velvety, consisting of coarse lobules which in turn had a fine lobulated surface. There was no ulcer crater or gross ulceration, but on the posterior surface of the bowel was an indurated area about one inch in diameter which was slightly raised above the level of the remainder of the tumor (Fig. 15—Gross specimen). The glands in the fat surrounding the tumor contained no carcinoma. Sections were cut through the entire thickness of the bowel wall through the indurated area (B), and at two places (A) in the soft part of the tumor. The tumor in the indurated area showed typical infiltrating adeno-carcinoma involving the muscularis and extending laterally under the mucosa (Fig. 17). In the soft tumor areas the microscopic picture was much like that described in the benign papillomatous lesions, except that mitoses were rather common as were hyper-chromatism of the nuclei (Fig. 16). Whether this tumor was malignant from its inception, as I believe, or whether we had a benign papilloma undergoing malignant degeneration is difficult to say. The clinical picture, however, determined the diagnosis of malignancy in face of contrary microscopic evidence.

Case VIII.—Male, age sixty. Came to Cook County Hospital for treatment of chronic myocarditis.

He was referred from a medical ward because of a protrusion and bleeding of bright red blood from the rectum.

Rectal examination revealed a round globular tumor mass about one inch in diameter situated on the mucosa of the anterior wall of the rectum, just above the muco-cutaneous line. This tumor was red in color, consisting of several coarse lobules which in turn were finely lobulated. The tumor was soft and spongy and had no induration at its base. It was removed under local anæsthesia by cautery, going well outside the tumor through the normal mucosa and beneath the tumor into the sub-mucosa. The patient made an uneventful recovery.

Microscopic examination of the tissue showed the tumor taking the place of the normal mucosa of the bowel. Only a slight amount of connective-tissue stroma was present in the tumor. Muscularis mucosa was everywhere intact and occasionally was elevated and ran into the tumor lobules as part of the connective-tissue stroma which was very fine and contained round-cell accumulations and thin-walled blood-vessels. The epithelium of the tumor was of both adenomatous and papillary types. The adenoma consisted of acini in the connective-tissue stroma with columnar cells containing basal nuclei. There were numerous goblet cells present in the epithelium. Other portions of the tumor consisted mainly of papillary projections with a sparse connective-tissue stroma covered with high columnar cells with basal nuclei. The muscularis mucosa was everywhere intact and there was no infiltrative characteristics seen in the tumor. The diagnosis is adeno-papilloma of the rectum.

Case IX.—Consists of material passed at bowel movement by a child. There was no history of the patient available.

The material consisted of three globular, finely lobulated tumor masses, without

pedicles, varying in size from ½ to 1½ cm. in diameter. They were soft and spongy and nowhere ulcerated. In color they were bright red.

The microscopic examination showed tumor tissue consisting of a connective-tissue stroma containing many blood-vessels, round-cell accumulations and wandering cells. In this stroma were typical adenomatous structures lined with low columnar epithelium with basal nuclei. There was little tendency to cyst formation. In other areas there were well-defined elongated papillary projections covered with columnar epithelium, with long, well-staining basal nuclei. A slight magnification of the microscopic slide showed the adenomatous and papillary structure of the tumor side by side (Fig. 13).

This tumor is, I believe, an adeno-papilloma with spontaneous expulsion of tumor fragments. The absence of a history and physical examination of the patient makes the diagnosis questionable.

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CARCINOMA OF THE BODY OF THE UTERUS*

A STUDY OF FIFTY CASES AT THE MASSACHUSETTS GENERAL HOSPITAL

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of Boston, Mass.

The cases upon which this report is based comprise all the microscopically proved cases of primary carcinoma of the body of the uterus which are recorded at the hospital between January 1, 1914, and January 1, 1925.†

Carcinoma of the body of the uterus is a disease entity quite distinct from carcinoma of the cervix, histologically and clinically. It is far less common than the latter. Statistics from the Mayo Clinic show the incidence of cancer of the body to be about one-third of that of cancer of the cervix. Norris's[1] figures for the University Hospital, Philadelphia, are about the same. Others place the relative incidence of fundus cancer very much lower.

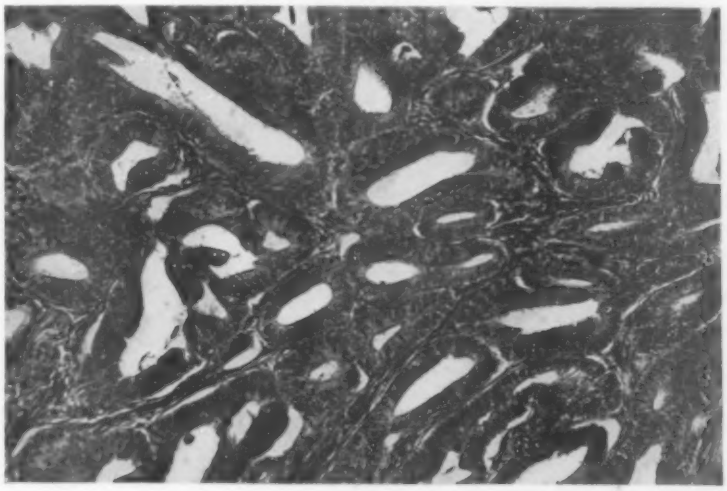

Fig. 1.—Photomicrograph of adenocarcinoma of uterus showing secondary cellular differentiation. Grade II. Patient living and well three years after operation. (Case E. S., 249376. Spec. 22-6-70.)

Carcinoma of the body of the uterus may be circumscribed or diffuse, but even in the advanced cases it rarely involves the cervical canal. It usually takes the form of papillary or polypoid outgrowths into the endometrial cavity which cause definite though moderate enlargement of the uterus. There is at the same time a tendency of the growth to invade the myometrium, the serosa may ultimately be reached with dissemination of the disease into the peritoneal cavity. Ovaries and tubes are frequently secondarily involved. The ovaries were involved in five of our cases (10 per cent.). Accompanying myoma was found in eleven of our cases (21 per cent.); this is about the proportion reported in other clinics.

* Read before the American Surgical Association, May 4, 1925.

† For the privilege of reporting these cases, grateful acknowledgment is made to the surgeons of the Hospital Staff.

Adenomyoma is also found in association with adenocarcinoma, and some authorities consider it to be an etiological factor of some importance. It was found but once in this series (Case W. S., 212268, Fig. 9).

Ewing [2] recognizes four types of carcinoma of the body:

1. Malignant adenoma—the most frequent type, in which there is giant reproduction of the uterine glands with little stroma.

2. Papillary adenocarcinoma—characterized by polypoid outgrowths.

FIG. 2.—Same specimen as Fig. 1, showing squamous cell. epithelium at tip of papillary process. An example of metaplasia. (Spec. 22-6-70.)

3. Alveolar carcinoma—a less common form in which the cells are packed in solid masses.

4. Adeno — acanthoma —a still rarer form in which squamous cells predominate over the glandular type.

There was no case of the latter in this series, but there were many specimens exhibiting extraordinary degrees of metaplasia from glandular epithelium to typical stratified epithelium composed of squamous cells with epithelial pearls, etc. There was one case of carcinoma of the body in which the primary growth in the uterus was of the alveolar carcinoma type, at autopsy definite squamous-cell infiltration of the retroperitoneal lymph-nodes was found (Case No. 242065).

Although the histogenesis of carcinoma remains uncertain, there undoubtedly is an early stage of the disease when it is limited to the mucosa. Ewing instances cases where curettings have shown carcinoma, and yet the extirpated uterus has shown no trace of the disease. This may also be explained on the hypothesis of the malignant transformation of a uterine polyp which has been completely removed by the curette. In this series there were two cases in which the curettings were reported as adenocarcinoma, and yet the uteri subsequently removed by operation showed no evidence of carcinoma. These cases cannot, however, be claimed as proved, as the specimens of the curettings have unfortunately been lost, and were not therefore subject to a critical review by Dr. H. F. Hartwell, the clinical pathologist, who has kindly gone

over all the specimens. These two inconclusive cases, therefore, in which the patients are living and well, are not counted among the "cures."

There have been no less than seven cases in which a uterine polyp was either present at the time of entrance to the hospital, or had been removed previously. The frequency of this condition suggests some etiological relationship, and certainly lends color to the hypothesis of the malignant degeneration of benign polyps.

That the type of cell plays an important part in the malignity of tumors has long been known, but the subject has been greatly advanced in the case of the epithelial tumors by the recent researches of MacCarty [3] and Broders.[4] Mahle [5] has studied the vast material of the Mayo Clinic in cancer of the body of the uterus, some 186 cases, with a view to grading the malignancy of the cases according to cellular differentiation. His studies show a very direct relationship of longevity to degree of differentiation.

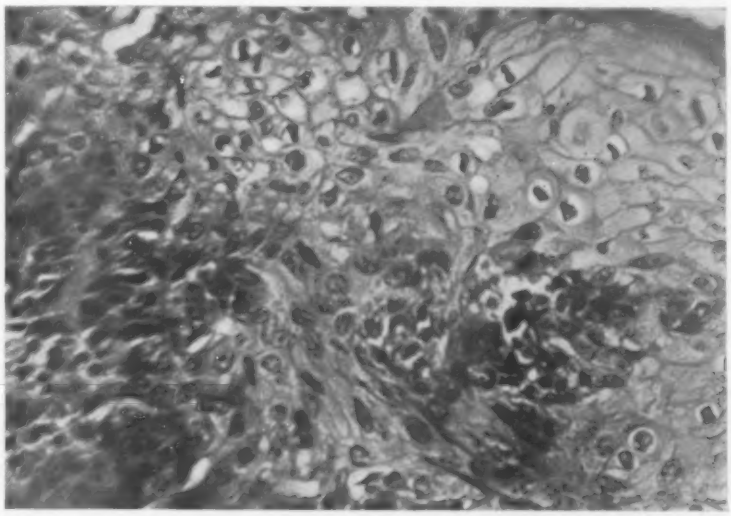

FIG. 3.—High power photomicrograph of Fig. 2, showing squamous epithelium. (Spec. 22-6-70.)

While other factors such as form and extent of growth, amount of myometrium invaded, involvement of lymph-nodes, duration of symptoms and general resistance of tissue, are of importance in forming a prognosis, Mahle believes that "taken as a whole, cellular differentiation appears to be the most important factor."

Dr. J. V. Meigs studied the microscopic specimens of thirty-eight cases in this series, from this viewpoint, without knowledge of the clinical histories. He placed twenty-nine cases in Grade II, three cases in Grade III, six cases in Grade IV, none in Grade I. While the clinical results in this small number of cases were found to be in general conformity with Mahle's deductions, there have been some very striking exceptions. Of the six cases in Grade IV—two are living and well three and a half years (Case E. S., 246011, Figs. 4 and 5) and two years, respectively, after operation, and another (Case E. S., 221686, Fig. 6) died of recurrence six years after operation, having enjoyed a period of five years of good health. The other three succumbed rapidly to the disease.

The average age of the patients in this series was fifty-four. Forty-two patients had been married. Thirty-two had borne children. Eight were single. Thirty-four, or nearly 70 per cent., had passed the menopause by more than one year.

The chief symptoms of the disease are hemorrhage and discharge. Abdominal pain of a colicky character, probably due to obstruction in the uterine canal, is often quite characteristic.

Hemorrhage and discharge coming on after the menopause is pathognomonic of cancer of the uterus, and yet how often are these telltale symptoms ignored by doctors as well as patients. The onset of bleeding after the establishment of the menopause for a year, means cancer nine times out of ten, and calls for an immediate and accurate determination of the cause.

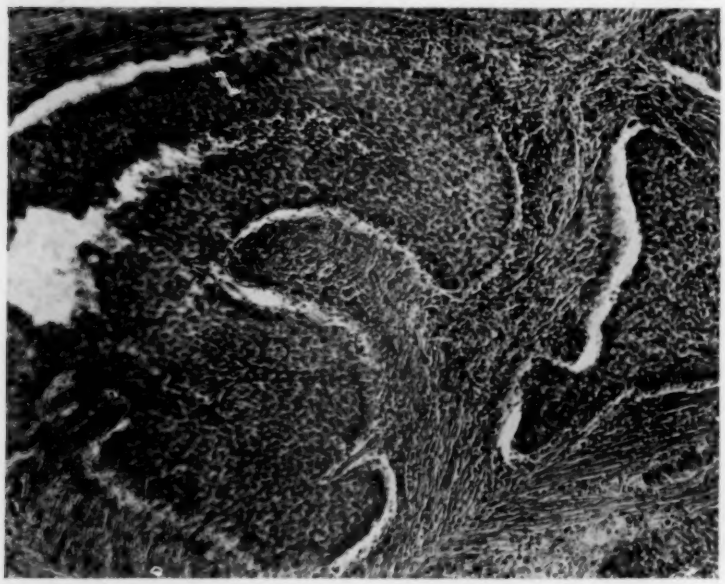

FIG. 4.—Adenocarcinoma of uterus showing area of primary cellular differentiation. (Spec. 21-10-114.)

There seems to be a widespread misapprehension among doctors that post-climacteric bleeding may be due to fibroids; this is very rarely indeed the case in my experience. In reviewing the histories of these cases the diagnosis fairly screams aloud in over half of them. There were no less than thirty cases in which post-climacteric bleeding had been going on for six months to four years or more. There were fourteen cases in which the post-climacteric bleeding had been noted for two years or more, and yet in this last group of cases there have been six three-year "cures" by operation, or 43 per cent. What a contrast this offers to carcinoma of the cervix in which a duration of symptoms of six months almost invariably spells the patient's doom.

In cases of carcinoma of the body of the uterus occurring before or at the time of the menopause, the diagnosis is much more difficult. Diagnostic curettage must be resorted to in all cases of doubt. Theoretically, curettage of a carcinomatous uterus seems undesirable not to say dangerous, but clinical experience seems to show that if hysterectomy follows immediately after, or

at most after an interval of not more than a few days, dissemination of the disease does not take place.

Norris has made a special study of this question, and his cases show an actual slightly greater percentage of cures with preliminary curettage, than in those in which immediate hysterectomy without curettage was done.

In our series, twenty-two cases had preliminary curettage, and twenty did not. In eight cases hysterectomy followed curettage immediately, being done at the same sitting. In thirteen cases hysterectomy followed after an interval of not more than a few days. There was one exceptional case in which there was an interval of fourteen months, during which time radium was used. Death resulted from recurrence three years after hysterectomy in this case. The end results in the cases subjected to preliminary curettage have been but slightly inferior to those in which it was not done. There were eight three-year "cures" in the former group, and ten in the latter.

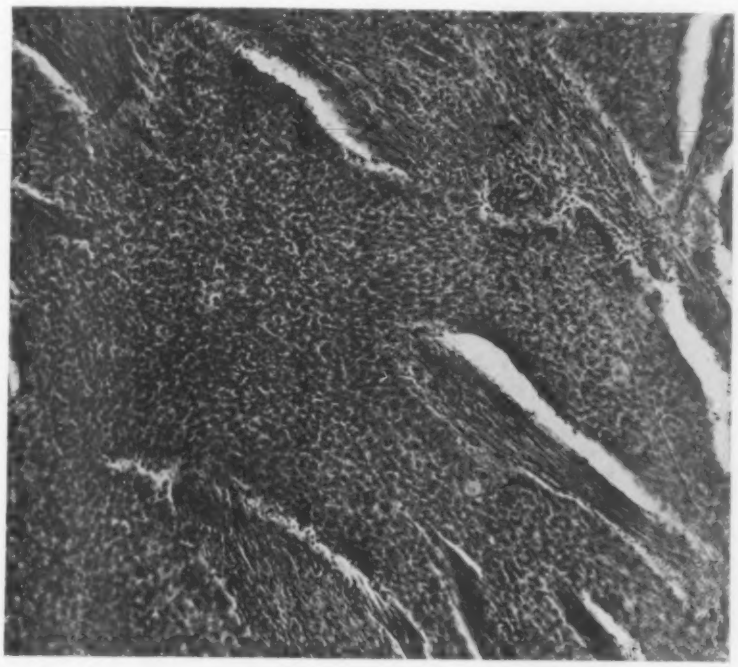

FIG. 5.—Same specimen as Fig. 4, showing area with no cellular differentiation. Such areas predominate. Grade IV. Patient living and well, three and a half years after operation. (Case E. S., 246011, Spec. 21-10-114.)

The diagnostic importance of preliminary curettage is so great, that in my opinion it should be resorted to in all doubtful cases, to be followed by immediate hysterectomy at the same sitting if the curettings are found to be positive. The practical advantages of an early and positive diagnosis outweigh the theoretical dangers of dissemination of the growth.

The accepted treatment of carcinoma of the body of the uterus is total hysterectomy with removal of the adnexa. There is some difference of opinion as to the relative advantages of the abdominal and vaginal routes. Personally I favor the former as a routine, on the ground that there is less traumatization of the tumor, and that intra-peritoneal complications such as adhesions, ovarian cysts, metastases to the ovaries, etc., can be more satis-

factorily dealt with. Vaginal hysterectomy has certain advantages in the obese and aged, and its results have been little if at all inferior to the other. The immediate mortality is slightly lower while the ultimate mortality is somewhat higher.

In this series of fifty cases, hysterectomy was done in forty-two. In three cases exploratory laparotomy disclosed inoperable conditions due to extension of growth or metastases. Four cases were treated with radium. One very advanced case was subjected merely to diagnostic curettage. The actual percentage of operability for the radical operation was eighty-four. This is strikingly high as compared to the operability of cancer of the cervix. In reviewing these cases, there was one case which was subjected to hysterectomy and resection of the sigmoid on account of invasion by the growth, which would generally be considered inoperable, and two cases subjected to radium treatment which would generally be considered operable. The other two radium cases were so treated on account of age and general debility rather than on account of any local contra-indication to operation. Only five cases out of the fifty were definitely inoperable from extent of the disease.

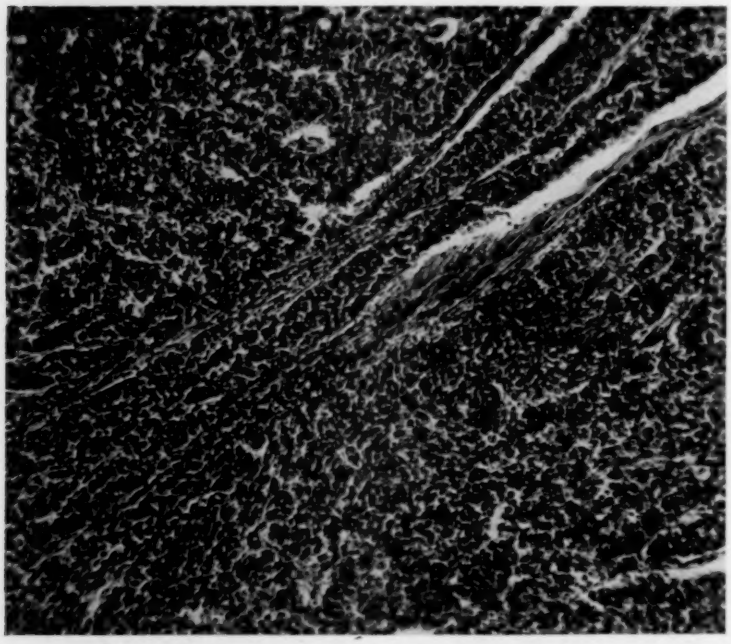

FIG. 6.—Adenocarcinoma of uterus showing no cellular differentiation. Grade IV. Patient died of recurrence six years after operation. (Case E. S., 221686, Spec. 18-4-71.)

Too few cases were treated with radium to permit of any definite conclusions. One patient who was not operated upon on account of diabetes, is reported to have died of internal hemorrhage a few days after radium treatment. This suggests the possibility of perforation of the uterus with intraperitoneal hemorrhage. One patient is living and well one year after radium treatment. One patient had three years of good health after radium treatment, but succumbed to the disease in the fourth year. On the whole, it seems that for the present, at least, in carcinoma of the fundus, operative

treatment should be preferred, being comparatively satisfactory both as to immediate and late results, with operability rate very high, while radium treatment on account of the location and nature of the growth is somewhat uncertain, and not without danger.

There were twenty-one total abdominal hysterectomies, eight vaginal hysterectomies, and thirteen supravaginal hysterectomies. There were four operative deaths, a mortality of 9.5 per cent. It may be said in extenuation of this high mortality, that in one fatal case a resection of the sigmoid which was secondarily invaded by the growth, was done at the same sitting. In another case the patient was a diabetic, and died in coma.

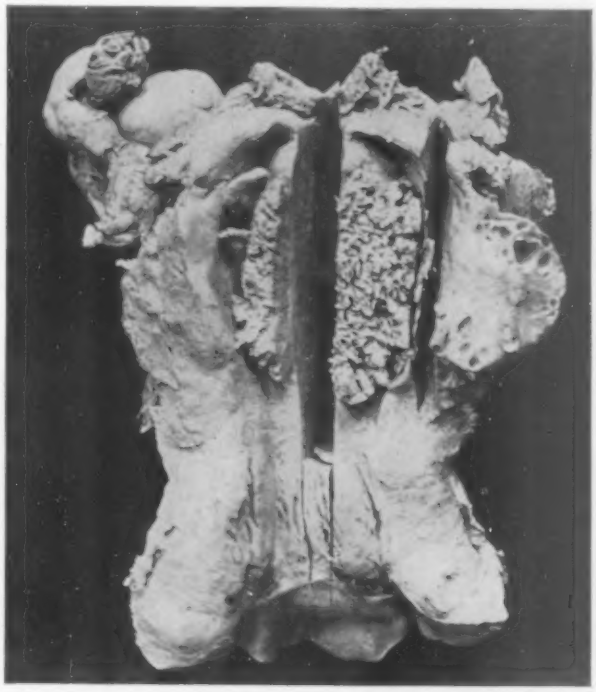

FIG. 7.—Circumscribed papillary adenocarcinoma of the body of the uterus. (Case E. S., 200758, Spec. 15-3-129.)

While probably few surgeons would advocate supravaginal hysterectomy as routine treatment for adenocarcinoma of the fundus, nevertheless it quite frequently happens that this incomplete operation is done. It is the result usually of error in pre-operative diagnosis. The surgeon believing that he is dealing with a case of simple myoma, makes no effort to remove the cervix, and if he is fortunate, it is not until the specimen is cut that the true condition is recognized. More often, unfortunately, the surgeon is made aware of the true state of things, when upon cutting across the cervical canal there is an exudation of soft carcinomatous material into the field of operation. He is then faced with the difficult problem of removal of an infected cervical stump. This happened in this series more than once. This unfortunate dilemma is to be avoided by preliminary curettage in all cases of fibroids, or other conditions in which supravaginal hysterectomy is contemplated. Figures show that myomata are found in 20 per cent. of cases of carcinoma of the fundus, and that carcinoma is found in about 3 per cent. of all myomatous uteri. Therefore it behooves us to be on the lookout for carcinoma in dealing with fibroids.

The gross character of the curettings will in many cases give the true diagnosis; where there is doubt, it is only necessary to wait for the report of

a frozen section which can be readily available before the stage of cervical removal is reached. The only other alternative is to perform total hysterectomy as a routine in all cases of fibroids, as recommended by several gynæcological authorities.

At the Massachusetts General Hospital, for the period of five years between January 1, 1917, and January 1, 1922, out of one hundred and twenty-three cases of cancer of the cervix, admitted there were eight cases of cancer of the cervical stump after supravaginal hysterectomy for fibroid tumors.[8] In four cases the original operation for fibroids had been done at this hospital, while in four others it had been done elsewhere. In five of these eight cases the early appearance of vaginal discharge and bleeding after the operation makes it very probable that the disease in the cervix was already coexistent at the time of operation. In fact, in one case the pathological examination showed this to be so.

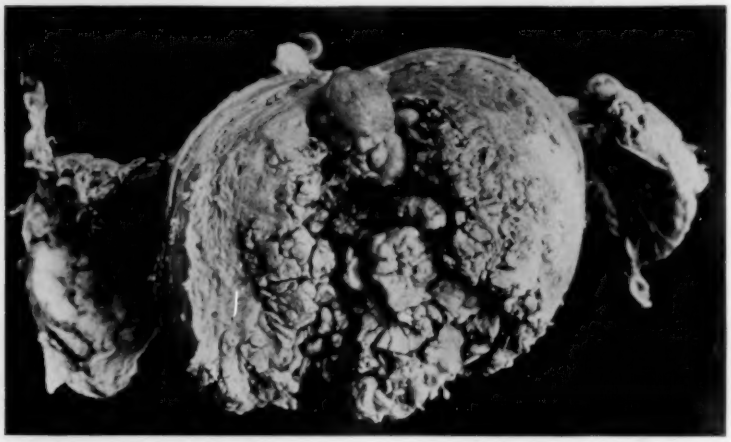

FIG. 8.—Diffuse papillary adenocarcinoma of the body of the uterus. Supravaginal hysterectomy in 1916. Patient free from recurrence in 1925. (Case W. S., 206886, Spec. 16-3-2.)

Undoubtedly there are many early cases of carcinoma of the body, in which the disease is sharply limited to a small area in the fundus, and in which supravaginal hysterectomy gives adequate removal as far as the growth itself is concerned, as our results seem to show. Six three-year "cures" in ten supravaginal hysterectomies, 60 per cent. There is no way, however, of accurately determining beforehand the limitations of the disease, and it is certainly not safe in the long run to take such chances. While supravaginal hysterectomy, combined with reaming out of the cervical canal with the knife or actual cautery, may be efficient in removing beginning carcinoma of the endocervix, my chief objection to the operation is the danger of contamination of the field from exudation of carcinomatous material, rather than the danger of incomplete removal of the growth.

Other important matters of technic in performing hysterectomy for carcinoma of the body of the uterus which I wish to emphasize are: (1) Avoidance of the use of tenacula in the fundus, traction should be made by means of clamps applied to the broad ligaments. (2) Preliminary ligation or clamping of the distal extremities of the tubes to prevent exudation of carci-

noma cells from the fimbriated ends. (3) Preliminary disinfection of the vagina and closure of the cervical canal by packing and suture to avoid possible exudation of infectious material from that source.

It was formerly generally believed that adenocarcinoma of the body of the uterus, treated by hysterectomy, yielded a very high percentage of "cures." Recent statistical studies from the Mayo Clinic,[5] the University Hospital, Philadelphia,[1] Lakeside Hospital, Cleveland,[7] and Free Hospital for Women, Brookline,[8] show percentages of "cures" varying from 30 to 62 per cent. Accurate comparison of these figures is not possible as they were compiled on somewhat different bases. It is to be regretted that the excellent formula for reporting results of operations for cancer advocated by Doctor Greenough[9] and approved by the American College of Surgeons has not been more universally adopted. The end results in this series of cases show 63 per cent. of three-year "cures" and 66 per cent. of five-year "cures," as set forth in Table I. This anomalous result illustrates the inconsistencies of statistics based on small numbers. It is, however, doubtless truer of carcinoma of the body of the uterus, than perhaps of carcinoma of any other organ, that if recurrence takes place at all it occurs early.

FIG. 9.—Papillary adenocarcinoma of the body of the uterus associated with diffuse adenomyoma. Total hysterectomy in 1916, patient living and well in 1925. (Case W. S., 212268, Spec. 16-12-63.)

CONCLUSIONS

1. In adenocarcinoma of the body of the uterus there seem to be some striking exceptions to the theory of the relation of cellular differentiation to malignancy.

2. Carcinoma of the body of the uterus is of relatively slow progression. It occurs at about the time of the menopause. After the establishment of the menopause the clinical diagnosis is usually quite obvious, before then it is often very obscure.

3. Diagnostic curettage should be resorted to in all doubtful cases.

4. Curettage followed shortly by hysterectomy does not seem to cause dissemination of the growth.

5. The frequent association of adenocarcinoma with myoma makes it imperative to perform preliminary diagnostic curettage whenever a supravaginal hysterectomy is contemplated.

6. Total abdominal hysterectomy is the operation of choice.

7. The operability rate and the results of operative treatment are such as to warrant a continuance of this form of treatment.

TABLE I

Carcinoma of Body of Uterus

End Results

A	Total number of cases 1914–1925	50
B	Reëntries	0
C	Recurrence from previous operation	0
D	Cases available for study of operability, mortality, etc.	50
E	Radical operation (hysterectomy)	42
F	Palliative operation (exploratory laparotomy)	3
G	No operation (curettage only)	5
H	Operative deaths (radical operation)	4
I	Operative mortality	9.5%
J	Operability (radical operation)	84%
K	Operability (all operations)	
L	Inconclusive cases, pathological examination of extirpated uterus failed to show carcinoma	2
M	Inconclusive cases (untraced)	0
N	Inconclusive cases, died within time limit without recurrence	1
O	Remaining cases available for three-year end-result data (entries previous to May, 1922)	36
P	Radical operations	30
Q	Palliative operations (exploratory laparotomy)	3
R	No operations (curettage only)	3
S	Number of cases alive and well—three years	18
T	Number of cases died after three years without recurrence	1
U	Number of three-year "cures" all operations	19
V	Number of three-year "cures" radical operations	19
W	Percentage of three-year "cures" all operations	52%
X	Percentage of three-year "cures" radical operations	63%
Y	Number of five-year "cures"	14
Z	Percentage of five-year "cures"	66%

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METASTATIC CARCINOMA IN THE URETER

ASSOCIATED WITH URETERAL STRICTURE

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Carcinomatous deposits from primary tumors in the pelvis are frequently found in the lymph-nodes along the iliac vessels and abdominal aorta, while metastasis to bone is of common occurrence, in a large number of reported cases, secondary nodules have been found in the lungs and liver, and in not a few instances metastasis has been noted in the kidney. With the lymphatics of the ureters communicating with those of the bladder, it is singular that the ureters escape the invasion of carcinomatous cells derived from uterus, prostate, or bladder. Garceau,[1] in 1909, was able to collect from the literature 13 cases of metastatic carcinoma in the ureter due to extension by continuity.

Owing to the fact that the writer can find but two cases [2, 3] in the literature giving metastasis to the ureter through lymphatic or blood stream, the following cases are reported:

Case I.—R. K., colored male, aged forty-seven years, admitted to University Hospital on September 19, 1922, and died on January 23, 1923.

Past History.—Frequent attacks of tonsillitis, acute colds and rhinitis, rheumatic fever eight years ago, duration two months. At this time the wrist, elbow and shoulder-joints were swollen, red and painful.

Present Illness.—In the fall of 1920 patient developed an infection of the genito-urinary tract, which commenced with a thin watery discharge followed by a purulent discharge for three weeks. The condition cleared up, but returned again at the end of one week; during this interval the patient suffered from no disability of any kind. A thin watery discharge appeared—nocturia every two hours during the night. On micturition pain over lower abdomen, which radiated down the extremities. First admission to hospital March 8, 1922, service of Dr. W. H. Toulson.

Cystoscopical examination revealed a carcinoma of the left wall of bladder. A suprapubic cystotomy was performed for cauterization of mass and radium implantation. Discharged June 26, 1922, improved. At the time of second admission to hospital, he complained of pain in the abdomen, thighs, legs and joints, with burning on urination. On October 23 a suprapubic urinary fistula appeared, discharging pus and urine.

Laboratory Findings.—Urine—repeated examinations showed specific gravity to vary between 1.010 and 1.015, albumin four plus; no sugar; large number of white blood cells and red blood cells; no casts. Average amount in 24 hours, 800 c.c.

Blood Picture.—Red blood cells, 3,000,000; leucocytes, 12,000; hæmoglobin, 60 per cent. (Talquist). Wassermann, negative.

Blood Chemistry.—Non-protein nitrogen 40 mgms.; urea, 21 mgms.; sugar, 100 mgms.

Autopsy No. 990—Genito-urinary Organs (Fig. 1).—Kidneys—Left—11.5 by 3.8 by 6 cm. Right—13 by 8 by 5 cm. The capsules strip with increased resistance, leaving an irregular surface, with numerous elevated nodules, which fluctuate. Several of these are torn open by stripping off the capsule, and they show a thick greenish-yellow exudate

within. On section all line markings are lost, and numerous cavities varying from 2 mm. to 10 mm. are seen; they contain a thick greenish-yellow exudate. The pelves and major and minor calices are dilated and filled with the same type of exudate.

Left Ureter—24 cm. in length—varies in diameter from 6 to 26 mm. and

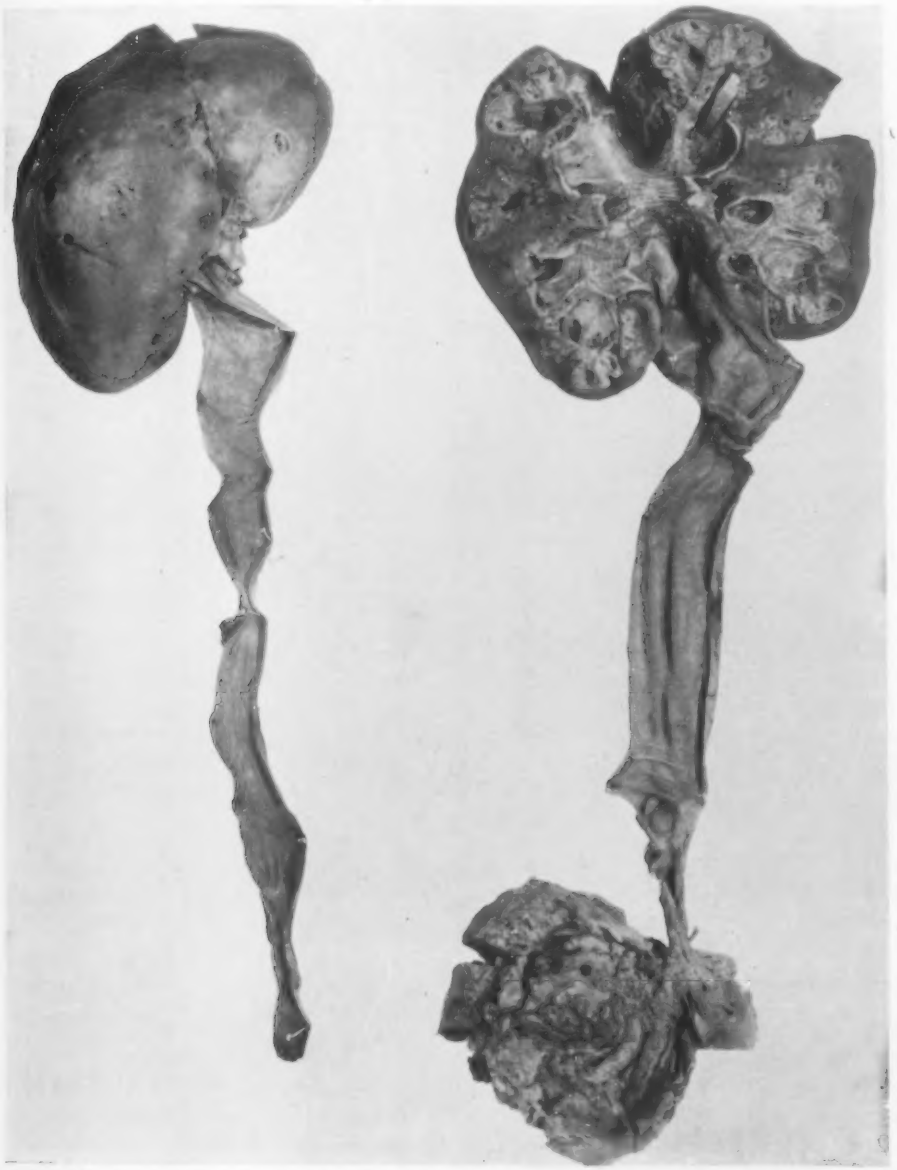

FIG. 1.—Case I. Kidneys, ureters and bladder.

shows its serous surface to be smooth and glistening. There is a kink 5 cm. below the uretero-pelvic junction, with a band of adhesions extending from the lower pole of the kidney over the anterior surface of this kink. On section the wall varies from 1 to 2 mm. in thickness. There is a stricture located 5 cm. below the uretero-pelvic junction which extends from the inner side across the lumen of the ureter for 8 mm. One cm.

below this a second stricture is seen extending from the outer wall toward the midline for a distance of 5 mm., which gives the lumen an S-shaped curve.

A tumor mass is seen 16 cm. below the uretero-pelvic junction; it is confined to the muscular wall and causes a narrowing of the lumen at this point.

A third inflammatory stricture is seen 4 cm. above the uretero-vesical orifice. The mucosa is of a yellowish-gray color and shows the vessels markedly distended by blood. There are two small soft calculi in the uretero-vesical orifice.

Right Ureter—24.5 cm. in length—varies in diameter from 6 to 24 mm. Its serous surface is smooth and glistening. On section the wall is seen to vary in thickness from 1 to 2 mm. At a point 6 cm. below the uretero-pelvic junction, a stricture is seen extending from the outer wall toward the midline for a distance of 7 mm. A second stricture is seen 5 mm. lower down, which extends from the inner side toward the outer wall for a distance of 5 mm., causing an S-shaped curve in the lumen of the ureter.

FIG. 2.—Case I. Microphotograph of tumor in left ureter, 16 cm. down.

A tumor mass is seen in the muscular wall 10 cm. below the uretero-pelvic junction, which constricts the lumen to 1 mm. in diameter. The mucosa is of a yellowish-gray color and shows the vessels of the tunica propria to be markedly distended by blood.

Bladder.—The wall on the left side and fundus measures 2.5 cm. on the right side, 1 cm. in thickness. The mucosa is visible on the right side, the remaining portion showing a rough ulcerating surface. The trigon is of a dark red color, with the ureteral orifices measuring 1 mm. The vesical orifice is grayish-red in color, and the mucosa cannot be made out.

Prostate.—The prostate is small, firm in consistency, nodular, and on section it is of a yellowish-gray color.

The testes, epididymes, vasa deferentia, and seminal vesicles show no noteworthy changes.

Anatomical Diagnosis.—Carcinoma of the bladder, with metastases to the prostate, ureters, mesenteric lymph-nodes, lumbar vertebra, and liver. Ureteral stricture, bilateral, left 3, right 2. Multiple calculi in the left uretero-vesical orifice; hydro-ureters, bilateral; hydronephrosis, bilateral; pyonephrosis, bilateral; adhesions between the lower poles of kidneys and ureters, with kinks in the ureters.

Microscopic Notes; Bladder.—Section from the wall shows a mass of fibrous connective tissue, which is infiltrated by large epithelial cells arranged in a disorderly fashion, many of which show mitotic figures. In some areas it is very poorly stained, so

that no cell outline can be made out. The layers of the bladder are not visible in any part of the section.

Left Ureter—(16 cm. down) Fig. 2. The muscular wall shows the muscle fibres and connective-tissue cells for the most part poorly stained, with a large number of epithelial cells, which are well stained, infiltrating in a disorderly fashion through the wall. Many of these cells show mitotic cell division. Three blood-vessels show their perivascular lymph-spaces filled with epithelial cells with clear cytoplasm and hyperchromatic nuclei. In the tunica propria, small round cells and polymorphonuclears are seen. The mucosa shows the transitional epithelial cells well preserved for one-half the circumference of the lumen.

Right Ureter (10 cm. down), Fig. 3—consists of a mass of poorly stained muscle fibres and connective-tissue cells which are replaced in areas by epithelial cells; in other areas epithelial cells are seen infiltrating in a disorderly fashion. Many of these cells show mitotic figures. Several blood-vessels show their perivascular lymphatics filled with the same type of tumor cells. The mucosa is absent.

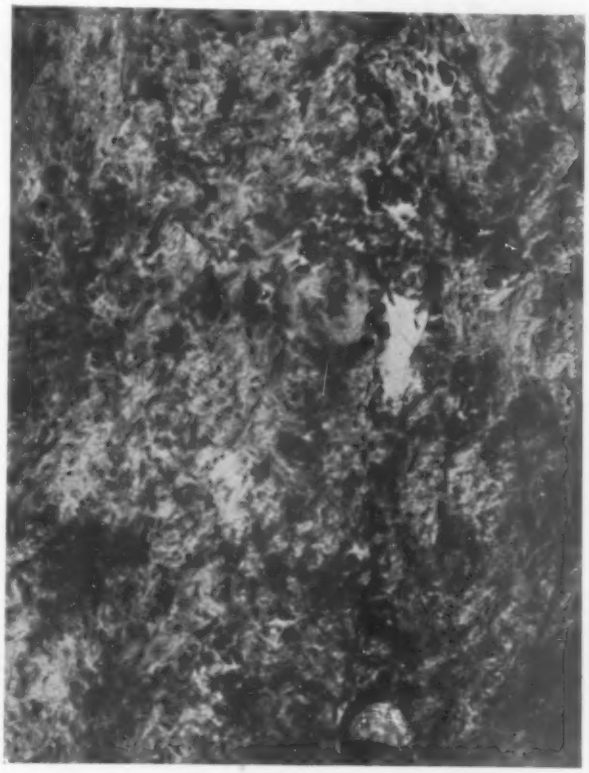

FIG. 3.—Case I. Microphotograph of tumor in right ureter, 10 cm. down.

Ureteral Strictures.—Sections from each show the muscular layer thickened due to an increase of connective-tissue cells between the muscle fibres. This is most pronounced in the inner half of the muscular layer and through the tunica propria. There is a marked infiltration of polymorphonuclears, mononuclear wandering cells and small round cells, with a few plasma cells. The mucosa shows the transitional epithelial cells well preserved in one area; in the remaining portion of the sections they are absent.

CASE II.—W. M., a white male, aged sixty-four years, admitted to Bay View Hospital, Medical Service, on June 24, 1924, with a history of having been treated at the Johns Hopkins Hospital for carcinoma of the prostate. Diagnosis on admission: Carcinoma of prostate, with metastasis to spine; empyema, right; cystitis; secondary anæmia.

The course in hospital was gradually downhill, and patient died on July 2, 1924.

Autopsy No. 2574.—Genito-urinary Organs (Fig. 4).—*Left kidney* 13.5 by 7 by 3.5 cm. Weight, 230 grams. The capsule strips with resistance, leaving a finely granular surface. On section the cortex is seen to vary from 4 to 8 mm. in thickness, with the striated lines in the cortex and pyramids indistinct in outline. The pelves and major and minor calices show a marked dilatation, with their lining mucosa of a dark reddish color.

Right Kidney—13 by 6 by 2.2 cm. Weight 180 grams. The capsule strips off with

resistance, leaving a pale granular surface. On section a large amount of fluid escapes. The cut surface shows the kidney substance to be reduced to a mere shell measuring from 4 to 8 mm. in thickness. The pelves—major and minor calices—are markedly dilated to form one large cavity. In the upper pole there is a tumor mass 3 cm. in

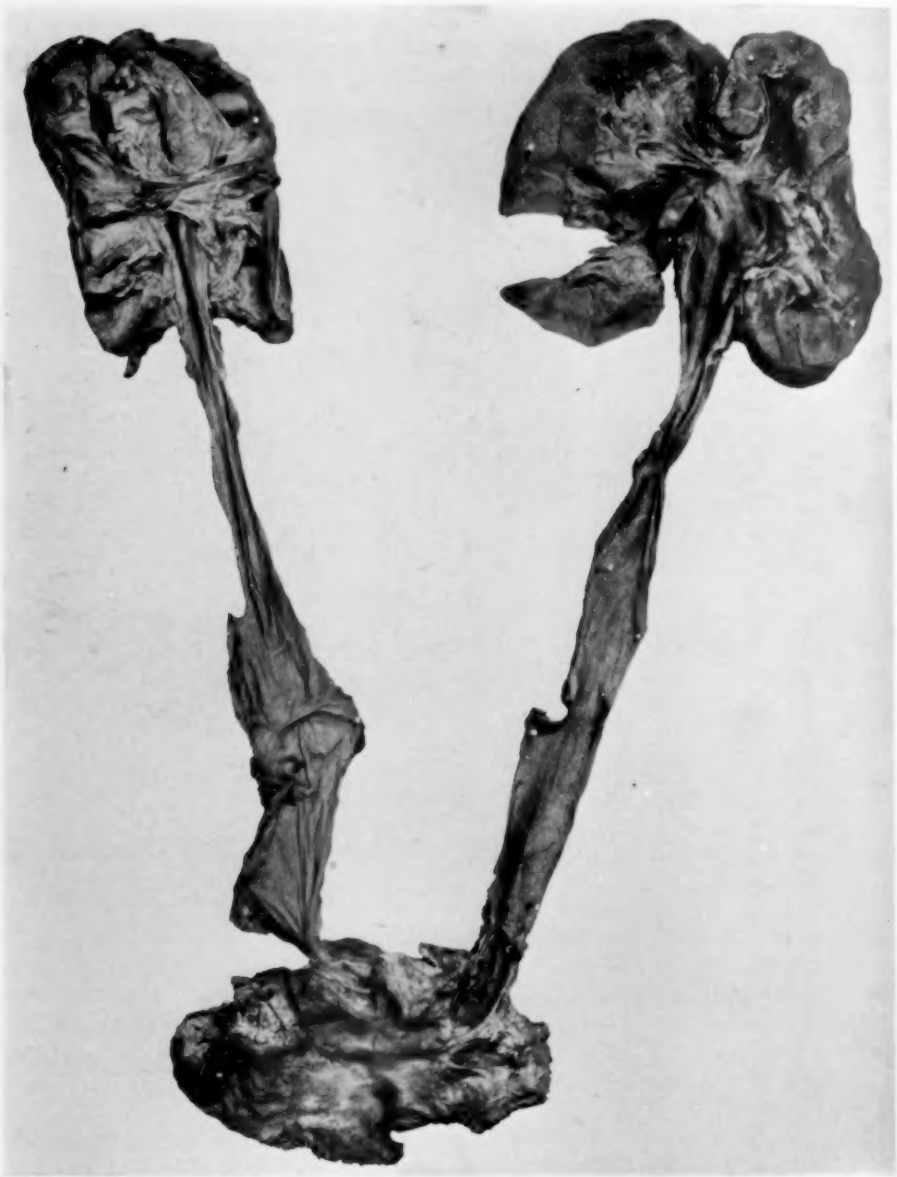

FIG. 4.—Case II. Kidneys, ureters, bladder, prostate and seminal vesicles.

diameter which extends from the pelvis to the cortical portion; it is composed of a number of grayish nodules.

Left Ureter—28 cm. in length—shows a marked dilatation from the bladder wall to kidney pelvis. On section the wall varies in thickness from 3 mm. to 6 mm. There

is a stricture 4 cm. below the uretero-pelvic junction, composed of scar tissue; a second stricture is seen 4 cm. above the uretero-vesical orifice, which is composed of scar tissue of the same appearance as the one above.

Right Ureter—28 cm. in length—shows a marked dilatation from bladder wall to kidney pelvis. On section the wall varies in thickness from 2 to 4 mm. There is a tumor mass 15 cm. below the uretero-pelvic junction, which is composed of a number of small grayish-white nodules, varying in size from 4 to 6 mm. This tumor mass involves the serous, muscular and mucous layers of the ureter. There is a stricture 3 cm. above the tumor mass, which is composed of scar tissue and extends two-thirds around the circumference and measures 3 mm. in thickness—10 mm. in depth.

Bladder.—The wall varies in thickness from 1 to 3.2 cm. The base and lateral walls are very firm in consistency and show numerous grayish-white nodules. The mucosa is of a grayish color, with the vessels markedly distended by blood. The right ureteral orifice cannot be seen. Upon opening the right ureter small nodules of a grayish-white color, measuring 1 to 2 mm. in diameter, are seen in the intramural portion.

Prostate is moderately enlarged and very firm in consistency. On section it is seen to be replaced by a tumor of grayish-white color made up of a large number of small nodules. This tumor mass can be seen extending into the base and lateral walls of the bladder, seminal vesicles, and vasa deferentia, and measures 8 by 7 by 5 cm. The vasa deferentia external to the internal ring show no gross changes.

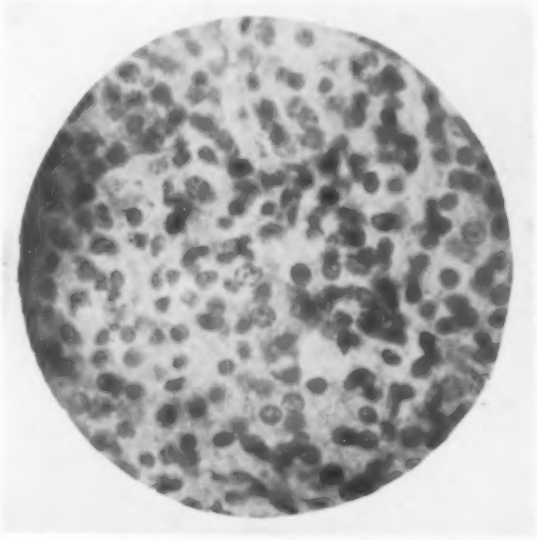

FIG. 5.—Case II. Microphotograph of tumor in right ureter, 15 cm. down.

Anatomical Diagnosis.—Adeno-carcinoma of the prostate with metastases to the bladder, seminal vesicles, vasa deferentia, right ureter, intramural portion and 15 cm. below the uretero-pelvic junction, right kidney, lungs, fifth lumbar vertebra, lymph-nodes along the external surface of ureters, iliac vessels, abdominal and thoracic aorta; ureteral strictures, bilateral; hydroureters, bilateral; hydronephrosis, bilateral; ureteritis, left; chronic diffuse nephritis.

Microscopical Notes: Prostate.—Sections from various parts of the gland show the alveoli to vary in size, and their lining epithelial cells vary from large clear columnar cells to small granular acidophile cells. A large number of the epithelial cells have hyperchromatic nuclei, a moderate number show mitotic cell division. In many areas these epithelial cells are seen breaking away from their basement membrane and infiltrating in a disorderly fashion through the connective tissue.

Bladder.—The muscular wall shows a large number of epithelial cells arranged as alveoli or in a disorderly fashion. These cells have hyperchromatic nuclei and a moderate number show mitotic cell division. Many of these cells are seen breaking away from their basement membrane. In this area the muscle fibres are absent or poorly stained; in a few areas the muscle fibres are well stained. The mucosa is absent in most areas. In one area the transitional epithelial cells are deeply stained, and there is a marked small round-cell infiltration in the submucosa.

Sections taken from the seminal vesicles and terminal 3 cm. of the vasa deferentia show them to be completely replaced by the tumor mass.

Ureter—Right.—15 cm. down (Fig. 5) shows the serosa to be infiltrated with epithelial cells, which have a clear cytoplasm and hyperchromatic nuclei. A few show mitotic division. The muscular layer is replaced by a tumor mass, which shows the same type of cells arranged as small alveoli or in a disorderly fashion. A large number of the cells have mitotic figures. At the edge of the tumor mass the epithelial cells can be seen infiltrating between the muscle fibres. The mucosa is replaced by small deeply stained epithelial cells with hyperchromatic nuclei.

Ureter—Right.—Stricture 3 cm. above tumor shows a mass of connective-tissue fibres which are well stained, with a few small round cells infiltrating between them. The blood-vessels are well preserved.

Ureter—Left.—Stricture shows the muscle fibres to be poorly stained with an increased amount of connective tissue between the muscle fibres, with a marked infiltration of small round cells and a moderate number of mononuclears and polymorphonuclears.

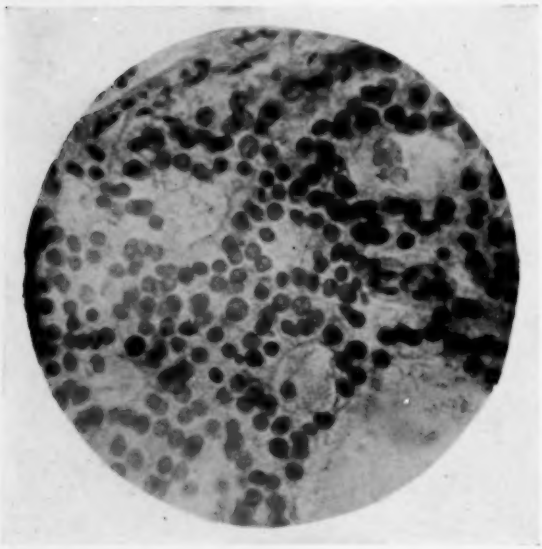

FIG. 6.—Case II. Microphotograph of right kidney-tumor.

Kidney—Right.—Section from tumor mass (Fig. 6) shows a large mass of well-stained epithelial cells with mitotic cell division, which for the most part are arranged as alveoli or glandular acini. There are a few well-preserved adult blood-vessels within the tumor mass. The cortex of right kidney shows a marked thickening of the capsule due to well-stained adult connective-tissue fibres. The capsules of Bowman show a marked thickening due to connective-tissue fibres. A large number of tufts are replaced by poorly stained fibrous connective tissue; others are completely hyalinized. The remaining tufts show the epithelial and endothelial cells well preserved, with their vessel walls thickened. The tubules for the most part show their lining epithelial cells well preserved with hyaline casts within the lumen. A number of tubules are seen collapsed in scar tissue which is infiltrated in areas by small round cells and mononuclear wandering cells. The larger blood-vessels show a thickening of their tunica intima.

CASE III.—S. B., admitted to Surgical Service of Bay View Hospital on November 16, 1923, and died November 4, 1924.

Past History.—Had childhood diseases, smallpox, typhoid, malaria, influenza and rheumatism. Had several hemorrhages from the vagina in the past two years, with a moderate loss of weight. Pain in lower abdomen for one month.

Physical Examination.—Blood-pressure 185/85. Patient is a fairly well-developed, poorly nourished, anæmic looking colored woman. Marked dental caries. Trachea diverted to the right side. There are a few moist râles at both bases. The heart rate is irregular. The abdomen is slightly full, no pain on palpation, no rigidity, no masses.

Vaginal Examination.—Moderate amount of pale reddish discharge. No ulceration or scarring of vulva. There are many small and firm painless nodules on the edges of the cervix and the anterior vaginal wall. The uterus is small, firm and painless.

Laboratory Findings.—Urine—specific gravity 1.018; albumin 1 plus; sugar negative. Microscopical—few granular casts. Blood—Wassermann negative.

Impression.—Carcinoma of cervix uteri, with metastasis to anterior vaginal wall.

Course in Hospital.—Patient had a gradual downhill course. Repeated vaginal hemorrhages, one of which required packing. Incontinence of urine.

Autopsy No. 2651—Genito-urinary Organs (Fig. 7).—*Left kidney* weighs 150 grams and measures 11 by 6 by 3.5 cm. The capsule strips with moderate resistance, leaving a pale, smooth surface. On section the normal architecture is fairly well preserved. The pelves and calices are moderately dilated.

Right kidney weighs 60 grams and measures 11.8 by 4.2 by 2.5 cm. The capsule is removed with ease. On section the cortex and pyramids are seen to be markedly thinned out, the line markings being scarcely visible. The pelves and calices are markedly dilated.

Left ureter shows a moderate dilatation from 1 to 1.8 cm. in diameter. On section the wall measures 1 to 2 mm. in thickness. The mucosa is of a dark reddish color throughout.

Right ureter is markedly dilated. On section the wall varies in thickness from 2 to 3 mm. A stricture is seen 3 cm. below the uretero-pelvic junction. A second stricture is located 13 cm. down which constricts the lumen to 1 mm. in diameter. There is a tumor mass in the muscular wall 15 cm. below the uretero-pelvic junction, which measures 7 by 10 mm. The

FIG. 7.—Case III. Right kidney and ureter.

ureter empties into the large cavity, at which point it is surrounded by a tumor mass.

Pelvic Organs.—Bladder: The muscular wall is markedly thickened, measuring from 8 to 12 mm. On the posterior wall there is a large opening which communicates with the vagina. The edges of this fistula tract are ulcerated in appearance. The mucosa is covered over with a grayish necrotic diphtheritic membrane.

The vagina is large, with the wall covered by a layer of grayish necrotic material. It is seen to open into a huge cavity, which communicates with the bladder anteriorly and with the rectum posteriorly.

The cervix and lower half of the body of the uterus has been destroyed by ulceration. The wall of this cavity is of a dark grayish-yellow color, irregular in outline. Numerous small tumor nodules are visible. At the upper part of this cavity, the fundus of the uterus can be made out. Loops of ileum are adherent to this cavity wall, walling it off from the peritoneal cavity. In the wall of the ileum a tumor nodule can be made out. Ulceration has extended on the right side to the ureter, so that it empties directly into the cavity. There is a large necrotic sloughing mass behind the levator ani.

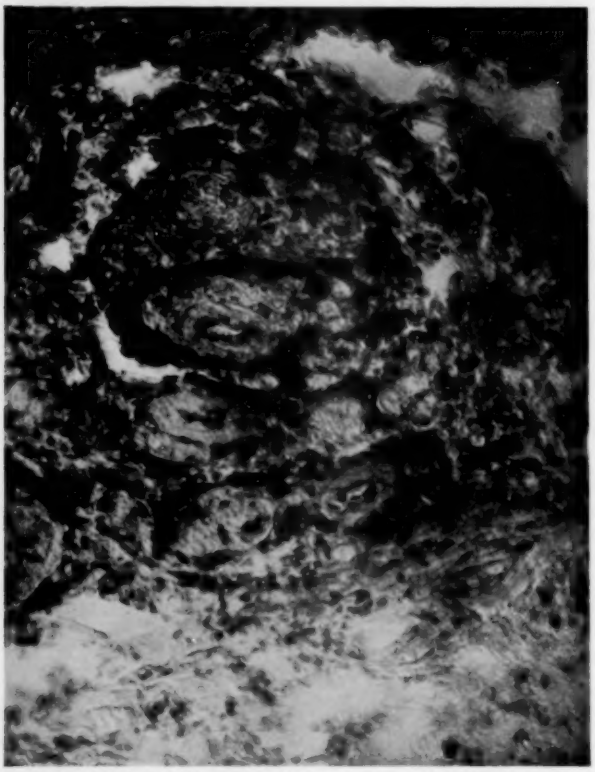

FIG. 8.—Case III. Microphotograph of right ureter, 15 cm. down.

The tubes and ovaries are so obscured by the large mass of adhesions that they cannot be identified.

Anatomical Diagnosis.—Squamous-cell carcinoma of cervix which has extended into the body of the uterus, posterior wall of the bladder, anterior wall of the rectum, distal end of right ureter, and wall of ileum; metastatic nodules in iliac and mesenteric lymph-nodes, right ureteral wall 15 cm. from pelvis, liver; fistula, recto-vaginal and vesico-vaginal; ureteral strictures, right (3 and 13 cm. down); hydro-ureters, bilateral; hydronephrosis, bilateral; arteriosclerosis; chronic diffuse nephritis.

Microscopical Notes.—Uterus: Section taken from ulcerating area shows a large mass of epithelial cells arranged in clumps, which are poorly stained. Several pearls are seen. The tumor cells are distinctly squamous in type and show mitotic cell division, with numerous ones containing hyperchromatic nuclei.

Ureter—Right (13 cm. down) shows the muscular wall to be covered with a single layer of mesothelial cells. There is a definite increase of connective-tissue cells between the muscle cells, replacing them in other areas next to the tunica propria. Throughout the muscular and tunica propria layers, small round cells and mononuclears are seen. The mucosa shows the transitional epithelial cells well preserved.

Ureter.—Right: Tumor mass (15 cm. down), Fig. 8, is surrounded by a capsule of

poorly stained connective tissue, which contains a few blood-vessels. The section shows the muscle fibres in a few areas to be fairly well preserved, with a few squamous epithelial cells infiltrating between them. In other areas epithelial cells are seen massed together, most of which have a clear cytoplasm and hyperchromatic nuclei, with a moderate number showing mitotic cell division. Several epithelial pearls are seen. The larger blood-vessels show a perivascular infiltration of small round cells and mononuclear wandering cells. Several nerve bundles are seen well stained. There are two blood-vessels, the perivascular lymphatics of which contain epithelial cells. These cells are the same in appearance as the tumor cells seen elsewhere. The mucosa is absent.

Discussion.—Langstaff,[4] Tanchau,[5] Gross,[6] Adams,[7] Thompson,[8] von Recklinghausen,[9] Cone,[10] Blumer,[11] Bumpus,[12] Kaufmann,[13] Young,[14] and others have reported the findings of secondary deposits from prostatic cancer, with a few cases showing sufficient infiltration into the bladder wall to obstruct the uretero-vesical orifice.

Giordano and Bumpus [2] reported a case of carcinoma in the uretero-pelvic junction, metastatic from the prostate, with the peri-ureteral lymph-nodes involved, and microscopic examination showed cancer cells in blood-vessels of the kidney nodule.

Thomas and Regnier [3] reported a case of cancer of the bladder with metastases to the lymph-nodes, psoas muscle, and right ureter, the muscular wall in the mid-portion being involved.

Cullen [15] shows excellent photographs of cancer of the cervix ulcerating through the lower end of the ureter as occurred in Case III, but makes no mention of metastatic nodules in the ureteral wall, the result of lymphatic metastasis.

Ewing [16] describes papillary tumors of the bladder extending into the lumen of the ureter or invading from the vesical wall, and primary tumors of the kidney pelvis extending down the ureter. In prostatic cancer Ewing states that the ureters are invaded from the vesical wall as in bladder carcinoma, or occluded by nodules at the orifice, or compressed by enlarged lymph-nodes.

In the above cases the tumor cells were found in the peri-vascular lymphatics of the ureters. Metastasis by blood is responsible for the nodules found in the liver and lumbar vertebra in Case I; lungs and vertebra in Case II; and liver in Case III.

The ureteral strictures—Case I, three in the left, two in the right; Case II—two in the left, one in the right; Case III, two in the right are essentially the same as those described by Hunner,[17, 18] Carson.[19]

CONCLUSIONS

(1) Three cases of metastatic carcinoma in the ureter are reported.

(2) From the bladder in Case I; prostate in Case II, and cervix uteri in Case III.

(3) In each case the cancer cells were found in the perivascular lymphatics of the ureter.

(4) Ureteral strictures, inflammatory in origin, were found in each case.

I am indebted to Professor Hugh R. Spencer for the privilege of reporting these cases.

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PRIMARY CARCINOMA OF THE DUODENUM*

REPORT OF FIFTEEN VERIFIED CASES

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A FAIRLY extensive review of the literature on the subject of primary carcinoma of the duodenum seems to show that there are comparatively few carcinomas of the small intestine, comprising only about 3 per cent. of those of the entire intestinal tract, and that the duodenum is usually affected more often than the jejunum or ileum. Surgical and necropsy records in the Mayo Clinic show the opposite to be true, there being fifteen cases of primary carcinoma of the jejunum, and nine of the ileum, making a total of twenty-four in contrast to fifteen of the duodenum. This difference may be accounted for partly by the fact that some of the cases of duodenal carcinoma reported in the literature are, as recent pathologic studies have shown, extensions from carcinoma of the pylorus.

Approximately 66 per cent. of carcinomas of the duodenum occur in the second or ampullary portion; 22 and 12 per cent., respectively, occur in the first, or supra-ampullary, and third, or infra-ampullary portions. In the Mayo Clinic series, six were in the ampullary portion, six in the supra-ampullary, and three in the infra-ampullary.

In the reported cases there were considerably more males than females, and the average age was fifty-two years. In our series twelve of the fifteen patients were males and the average age was fifty-six years. Half of the patients were in the fifth decade of life; only three were in the fourth. The youngest patient was thirty-nine, and the oldest seventy.

Symptoms.—The clinical picture, according to many earlier, as well as later, writers, depends on the location of the growth. Thus with carcinoma of the first or supra-ampullary portion of the duodenum, the symptoms common to carcinoma or obstruction of the pylorus are simulated. Involvement of the ampullary portion is supposed to give rise to an obstructive form of jaundice with its sequelæ, often to infectious processes in the bile ducts, or abscesses in the liver, so that the picture can hardly be distinguished from that of carcinoma of the head of the pancreas, bile ducts or ampulla. Deaver and Ravdin modify the traditional description somewhat by asserting that jaundice, under the circumstances, is a constant and persistent symptom,

* Read before the American Gastro-enterological Association, May 25, 1925.

although not so severe as with carcinoma of the ampulla; that with carcinoma of the third or infra-ampullary portion the symptoms are those common to malignant pyloric obstruction except that invariably there is no palpable mass, and the vomitus is much more profuse, and contains bile and pancreatic juice. There are, also, the systemic changes that result from obstruction and the loss of a great deal of fluid. Certain observers have also noted the presence of free hydrochloric acid in the gastric contents. The latter, however, is of no differential diagnostic significance, as free hydrochloric acid may be present in cases of obstructing pyloric cancer. In all varieties the symptoms are chiefly gastric and are those usually associated with carcinoma of the pylorus, although often less pronounced. Until recently the diagnosis has been rarely made during life, or before operation, and even with the aid of Röntgen-ray examination it is often very difficult to recognize the disease.

Clinical Symptoms.†—In the series of fifteen cases the mode of onset was recorded as gradual in seven, and as sudden in eight. The initial symptom in seven was pain, usually epigastric and moderate in degree. In only two cases (Table II, Cases VI and VII) was it both severe and sudden and an outstanding feature throughout the complaint. In the remainder the initial symptom was that of a moderately reversed peristalsis, or retention, ranging from flatulency and its accompanying subjective sensations to vomiting of the obstructive type. In eleven cases the pain was a prominent primary or secondary feature. In three the pain was negligible or absent. In ten cases the pain appeared from one to four hours after meals, usually two to three hours afterward. Vomiting, which was a common symptom, usually afforded relief. Two patients obtained relief by taking alkalis. In the majority of cases, therefore, the syndrome of duodenal ulcer was apparent, but the onset of the disease in later adult life, its rapidly progressive character as a rule, the presence of marked pyloric obstruction and the frequent subacid or anacid gastric contents, and finally the general appearance of the patient, implied that we were dealing with a more serious process. The average duration of symptoms at the time the patients presented themselves for examination was six and one-third months. Two had had symptoms for only seven weeks, yet both had advanced duodenal obstruction. One patient (Table II, Case XI) had had symptoms for about fourteen months, the longest in our series. He also had advanced duodenal obstruction and at operation a hard, movable mass was found from 6 to 8 cm. below the pylorus, encircling the duodenum. Somewhat to our surprise the patient was still alive thirteen months after a posterior gastro-enterostomy had been performed. The average duration of life in the entire series was thirteen and thirty-six hundredths months. The average duration of life, as recorded in the literature, is about

† The clinical records are fairly complete in fourteen of the fifteen cases. The one exception was a necropsy case (Table II, Case IV), in which there was a carcinoma of the duodenum, apparently having its inception in an old scar of a duodenal ulcer, but with an independent associated carcinoma of the pancreas; symptoms were chiefly due to the latter.

seven months, the extremes ranging from three to eighteen months. Flatulency, characterized by bloating, belching, and a sense of epigastric fullness, the latter often provoking distress, pain as previously noted, nausea and vomiting, usually of the retention type, and relief by vomiting, were the chief symptoms common to all the patients. Weakness, thirst, dehydration, toxæmia, and marked loss of weight and strength were symptoms in the cases of advanced obstruction. With few exceptions the clinical course was quite progressive, which is to be expected in view of the rather short average duration of the disease. Jaundice, in our cases, contrary to those recorded in the

TABLE I.

Case A498518. Duodenal Toxæmia of Carcinoma.

	Intake, c.c.					Output, c.c.				Blood chemistry				Blood pressure	
Date, 1925	Proctoclysis	Subcutaneous	Intravenous glucose 10% NaCl 1%	Mouth	Total	Total	Emesis	Lavage	Urine	Urea	Chlorids	Carbon dioxide combining power	Hæmoglobin, per cent.	Systolic	Diastolic
3–10	On Admission									60	310	121.5	80	90	66
3–11	1300	0	2000	1780	5080	4210	1090	2050	1160	36	350	124.1	79	95	70
3–12	1000	0	2000	0	3000	2210	400	625	1175	26	380	113.8		98	70
3–13	2500	0	2000	90*	5590	2325	0	1025	1300	26	450	103.4	70	90	60
3–14	2500	0		90*	2590	2325	0	1625	700	28	450	105.2	63	95	65
3–15	1500	0	1000	90*	2590	3600	0	2350	450					95	65
3–16	1000	0	3000	90*	4090	3200	0	1600	600	22	460	94.8	65	95	55
3–17	Operation—posterior gastro-enterostomy														
3–17										20	540	83.0			
3–18										45	500	82.0			
3–19										39	500	68.0			
3–20										24	460	63.0			

*Belladonna.

literature, was conspicuous by its absence with carcinoma of the ampullary portion, at least while the patients were under observation. However, it is reasonable to suppose that obstructive jaundice was one of the prominent terminal conditions, and probably the actual cause of death. The fact that the seriousness of jaundice in the second group is so strongly stressed by other writers leads us to believe that the patients were seen in an advanced stage, or that the carcinoma had its origin in the ampulla itself or in the terminal portion of the common duct. Carcinoma of the head of the pancreas occasionally involves the duodenum sufficiently to produce obstruction, thus confusing the diagnosis.

TABLE II.
Summary of Cases.

Case	Symptoms	Examination	Laboratory data	Operation	Results
1	Indigestion ten years. Recent trouble, gradual, seven weeks duration. Dull epigastric pain one hour after meals. Distress and pyrosis. No vomiting	Cachexia 2. Right epigastric tumor, small, nodular, movable. Lost 2 pounds in weight	Total acids 94, free hydrochloric 0, lactic 2, blood 2, food remnants 4. Röntgenograms not made	Operation, June 12, 1920. Carcinoma of duodenum, extending up to pylorus, with obstruction. Anterior gastro-enterostomy	Died three months after operation.
2	Gradual onset one year previously. Flatulency, also epigastric pain two hours after meals. Vomiting of retention type. Progessively worse	Pallor. Tumor of right epigastrium. Visible peristalsis. Weight loss, 40 pounds	Total acids 36, free hydrochloric 8, lactic 2, blood 2, food remnants 3. Second examination: total acids 24, free hydrochloric 0. Röntgenograms not made	Operation, November 22, 1911. Carcinoma in pyloric end and lesser curvature of stomach. Primary malignant papilloma. Pylorus and duodenum resected. Mikulicz-Billroth No. 2; gastro-enterostomy	Lived two years after operation.
3	Sudden onset twelve months before. Numbness in upper and lower extremities. Dyspnœa on exertion. Spell of epigastric distress three hours after meals and at midnight. Flatulency and pyrosis. Suggestive retention type of vomiting	Anemia. No tumor palpable. Loss in weight 13 pounds. On second examination ten months later, severe anemia and jaundice	Hæmoglobin from 40 to 55 per cent. Erythrocytes, 280,000. Total acids 10, free hydrochloric 0, 20 c.c. of gastric contents. Röntgenogram indeterminate. Urinalysis normal. Ten months later hæmoglobin 22 per cent.; erythrocytes, 1,790,000. Röntgenograms not made		No operation. Died. Necropsy: carcinoma of first portion of duodenum, involving head of pancreas, with partial occlusion of common bile duct.
4	Syndrome of primary carcinoma of head of pancreas	Icterus. Fixed tumor to right of umbilicus. Emaciation. Loss of weight, 20 pounds	Hæmoglobin from 60 to 70 per cent. Erythrocytes, 4,680,000. No gastric analysis. Coagulation time nine to eleven minutes. Röntgenograms not made		No operation. Died. Necropsy: carcinoma of head of pancreas with obliteration of ampulla; carcinoma of duodenum 2.5 cm. in diameter, apparently arising in scar of healed duodenal ulcer.

5	Gradual onset, eight months' duration. Dull, gnawing pain in epigastrium, from two to four hours after meals. Flatulency. Relief by frequent and copious vomiting. Constipation marked	Tenderness of right epigastrium. Marked loss of weight and strength. Loss of weight, 42 pounds	Hæmoglobin 75 per cent.; erythrocytes, 4,800,000. Total acids 30. Free hydrochloric 0. Food remnant 400 c.c. Occult blood 1. Röntgenogram showed duodenal ulcer	Operation, September 15, 1917. Posterior gastro-enterostomy	Duration of disease eight months. Died. Necropsy: carcinoma of supra-ampullary portion of duodenum, with ulceration of mucosa.
6	Sudden onset seven weeks before. Severe epigastric pain. Vomiting of retention type. Rapidly progressive course	Moderate anemia. Rigidity throughout epigastrium. Loss of weight, 30 pounds	Hæmoglobin 75 per cent. Erythrocytes 4,700,000. Total acids 58, free hydrochloric 10; 1127 c.c. of gastric contents. Food remnant 3, blood 1. Röntgenogram showed lesion at outlet of stomach; retention 4	Operation, April 22, 1920. Posterior gastro-enterostomy. Tumor situated 1 inch below the pylorus, rather fixed	Died nine months after operation. Duration of disease about eleven months. Terminal signs: obstructive jaundice.
7	Sudden onset three months before. Attacks of flatulent epigastric distress, followed by severe pain. This appears irregularly after meals; duration one to two hours; relief by vomiting, obstructive type	Anemia. Malnutrition. Movable and tender tumor just below umbilicus. Lost 55 pounds in weight in two months	No test-meal or X-ray. Urine showed a trace of albumin and a few hyalin casts	Operation, July, 1913. Contracting type of tumor in second portion of duodenum, 4.5 inches below pylorus. Gastro-enterostomy. Primary operation performed eleven days before for pelvic tumor	Lived about eight months after operation.
8	Sudden onset seven weeks before. Severe pain in right upper quadrant. Nausea, flatulency, vomiting of retention type. Intermittent attacks, progressively more frequent. Pain appears from two to three hours after meals. Food ease	Succussion splash. Lost 27 pounds in last year	Hæmoglobin 66 per cent. Total acids 28, free hydrochloric 20, food remnant 1, 365 c.c. of gastric contents. Röntgenogram was negative	Operation, February 17, 1919. Posterior gastro-enterostomy. Hard, nodular mass about 4.5 inches below pylorus, encircling duodenum just above ampulla, producing obstruction	Died one year after operation. Duration of disease, two years. Severe obstructive jaundice and dyspnœa developed prior to death.

TABLE II—Continued.
Summary of Cases.

Case	Symptoms	Examination	Laboratory data	Operation	Results
9	Duration of symptoms four months; sudden onset. Aching pain in epigastrium from two to three hours after meals; flatulency; obstructive vomiting. Duodenal toxæmia and recent tetany	Moderate anemia, malnutrition, visible gastric peristalsis and succussion. Tumor in lower right epigastrium, movable. Acute nephritis. Blood area, 120-124 mg. Creatinin, 1.7 to 2.3 mg. Albumin and casts in urine. Loss of weight, 40 pounds	Hæmoglobin 76 per cent. Erythrocytes 4,590,000. Total acids 26, free hydrochloric 14, 700 c.c. of gastric contents; trace of blood, food remnant 1. Second test: total acids 18, free hydrochloric 0, 750 c.c. of gastric contents. Fasting contents: total 10, free hydrochloric 0, 100 c.c. gastric contents. Röntgenogram showed large gastric residue, gaping pylorus, distended duodenal cap, obstruction beyond	Operation, October 2, 1920. Apparent acute obstruction in duodenum about 8 cm. below pylorus. Hard mass involving head of pancreas. Posterior gastro-enterostomy	Died two days after operation. Necropsy: primary carcinoma of duodenum with obstruction. Bilateral broncho-pneumonia and acute diffuse nephritis.
10	Duration five months. No actual pain. Flatulency, dull ache with epigastric fullness. Gnawing sensation in epigastrium two to three hours after meals. Emesis only once in spite of obstruction	Anemia. No palpable mass. Visible peristalsis. Succussion splash. Loss of weight, 8 pounds	Hæmoglobin 59 per cent. Erythrocytes 3,600,000. Total acids 30 to 70, free hydrochloric 0, 790 c.c. of gastric contents. Food remnant 3, occult blood 2. Röntgenogram showed large stomach, much secretion. No demonstrable pathologic lesion	Operation, November, 1922. Carcinoma of duodenum at ampulla, causing obstruction	Lived eleven months after operation. No knowledge of terminal symptoms.
11	Gradual onset fourteen months before. Gas, occasional slight pain in epigastrium. Vomiting of retention type. Loss of weight and strength	Fair color. Malnutrition 3. Abdominal distention, visible gastric peristalsis. Loss of weight, 50 pounds	Hæmoglobin 80 per cent. Erythrocytes 4,610,000. Total acids 54, free hydrochloric 20, food remnant 2. Yeasts and Oppler-Boas. Röntgenogram showed stomach and duodenum dilated 3. Blood chemistry of duodenal toxæmia	Operation, February, 1923. Obstruction of duodenum by hard, movable tumor, 6 by 5 by 5 cm., from 6 to 8 cm. below pylorus. Encircling type. Posterior gastro-enterostomy. Large dilated colon, much gas	Patient was alive eleven months after operation.

12	Sudden onset two months before. Vomiting, gas, epigastric pain with nausea one or two hours after meals. Later severe gastric tetany and duodenal toxæmia	Fair color. Malnutrition. Scaphoid abdomen. Borborygmus. Visible peristalsis. Toxic, dehydrated. Chvostek and Trousseau positive. Loss of weight, 50 pounds	Hæmoglobin 83 per cent. Erythrocytes 4,090,000. Patient too ill and toxic for tubing or X-ray. (See Table I for data on duodenal toxæmia.)	Operation, March, 1925. Carcinoma in lower, second portion of duodenum, with marked obstruction. Collapsed jejunum. Posterior gastro-enterostomy	Living. Vomiting and bloating occasionally.
13	Gradual onset two months before. Belching, pyrosis and regurgitation followed in a week by emesis. No pain. Dull, heavy sensation in epigastrium	Color fair. Malnutrition 1. Succussion splash. Loss of weight, 10 pounds	Hæmoglobin 75 per cent. Erythrocytes 4,600,000. Total acids 24, free hydrochloric 12, 1000 c.c. of gastric contents, food remnants 2, bile 2. Röntgenogram showed dilated stomach and duodenum. Obstruction 6 inches below pylorus	Operation, November 24, 1920. Small, hard tumor at duodeno-jejunal angle, producing very marked obstruction. Gastro-enterostomy	Lived thirteen months after operation. Obstructive jaundice and diarrhœa.
14	Gradual onset nine months before. Darting pain in epigastrium soon after meals. Gas. Later obstructive vomiting. Progressive course	Cachexia. Distention and tympany in upper abdomen. Loss of weight, 50 pounds	Hæmoglobin 56 per cent. Erythrocytes 3,500,000. Total acids 50, free hydrochloric 34, 100 c.c. of gastric contents. Röntgenogram was negative	Operation, May, 1921. Exploration. Abdominal carcinomatosis	Died two days after operation. Necropsy: carcinoma of terminal duodenum with metastasis to jejunum and ileum.
15	Sudden onset of symptoms two months before. Moderate epigastric pain, nausea and vomiting. Progressive course	Moderate anemia. Epigastric tenderness. Loss of weight, 15 pounds	Hæmoglobin 69 per cent. Erythrocytes 4,100,000. Total acids 8, free hydrochloric 0, 500 c.c. of gastric contents, food remnants 3. Röntgenogram showed operable gastric cancer, retention 2	Operation, February, 1921. Carcinoma involving terminal duodenum, with obstruction. Duodeno-jejunostomy	Died seven days after operation. Necropsy: carcinoma of duodenum, 20 cm. from pyloric ring. Lumen obstructed 3. Bilateral bronchopneumonia. Diffuse fibrinous peritonitis.

On physical examination a tumor was found in five (33.33 per cent.) of the fifteen cases in the series. Three of the cases were in the group of six cases of carcinoma of the first, or supra-ampullary portion of the duodenum. The remaining two were in the second or ampullary group, which also consisted of six cases. In the first group of three cases the tumors were rather tender, somewhat mobile, firm, nodular, and moderate in size. No palpable mass was found in the third or infra-ampullary portion. An anemic, cachectic appearance was the rule. One patient (Table II, Case III) had a severe terminal anemia. Data concerning terminal symptoms and signs in patients who survived operation but who later died at their homes are very incomplete, but it is assumed that obstructive jaundice, inanition, toxæmia, anemia, extensive metastasis, infectious processes, intercurrent disease, or other complications were the culminating factors.

Gastric Retention from Duodenal Obstruction.—There was clinical evidence of duodenal obstruction in twelve cases, consisting of a retention type of vomiting, marked succussion splash, and visible gastric peristalsis; the retention was readily confirmed by motor-meal tests. In two other cases (Table II, Cases III and XIV), there was no retention on first examination, but examinations four and nine months later, respectively, revealed marked obstruction and physical deterioration. Therefore, in only one case (Table II, Case IV) was there no duodenal obstruction with its associated phenomena. Gastric analyses were made in twelve cases. In two cases the precarious condition of the patient, largely on account of obstructive vomiting, did not permit gastric analysis or Röntgen-ray studies. In five of the twelve cases there was an absence of free hydrochloric acid. In the remaining seven free acid (from eight to thirty-four, in terms of tenth normal sodium hydroxid, with an average of seventeen) was present in the gastric content. In all but one case in which there was free hydrochloric acid there was also gastric retention. Positive occult blood reactions were obtained in most cases. In the infra-ampullary group the secretion was excessive and the gastric contents were colored a green or yellow by the presence of bile and pancreatic juice. There was no particular difference in the gastric chemistry and motor function in the various groups.

Röntgen-ray Examination.—In three of the ten cases in which röntgenograms were made the findings were negative or indeterminate. In two of these the examination had been made before obstruction had developed. In one case (Table II, Case VIII), in which there was no barium residue after six hours, the Riegel meal revealed gastric retention after twelve hours. Dilated stomach, with moderate to marked retention, but without a demonstrable lesion in the stomach were the common findings and were occasionally diagnosed as operable lesions of the stomach. In two cases the demonstration of a large stomach, dilated duodenum and retention made an exact anatomic diagnosis possible by this procedure. Data of individual cases may be found in Table II.

Toxæmia from Duodenal Obstruction: Treatment.—Toxæmia from duodenal obstruction is a serious complication because of its direct bearing on prognosis and surgical mortality. Clinically, toxæmia may be suspected when the vomiting is associated with, or followed by, evidences of dehydration, symptoms of shock and uremia, and tetany-like manifestations. The characteristic changes in the blood are a rise in the blood urea, a fall in the plasma chlorids and a rise in the carbon dioxid combining power of the blood plasma. In this type of intoxication the invariable tendency is towards alkalosis, and therefore the use of alkalis in the treatment is contraindicated, although severe toxæmia may exist without tetany. The latter, which is a very disturbing complication, may ensue when the carbon dioxid combining power of the plasma rises above 100 per cent. It is mainly by a study of the chemistry of the blood that the condition can be recognized early, the severity measured, and the extent of treatment gauged and its effect determined. Sodium chlorid, glucose and water, given intravenously in the severe cases, constitute the accepted and only effective method of treatment. Repeated gastric lavage should be the exception, rather than the rule, to obviate the additional loss of fluids and chlorids, of which the tissues are greatly in need. A patient, who came under our observation in 1920 (Table II, Case IX), developed severe toxæmia as evidenced by urinary changes, nitrogen retention, dehydration, shock, low blood pressure, and finally tetany. The patient died after a gastro-enterostomy had been performed, although we realized at the time that the risk was very great. The second patient (Table II, Case XII) was observed in March of this year. He had marked duodenal obstruction, complicated eventually by profound toxæmia and tetany. Treatment enabled the patient to undergo and survive the operation successfully (Table I). The fact that an intolerable situation is relieved and the life of the patient prolonged by gastro-enterostomy, even though it is only a palliative measure, makes such pre-operative preparation a vital procedure.

Differential Diagnosis.—Because of the rarity of the disease it is reasonable to assume that the condition may sometimes be overlooked. It is almost impossible to distinguish, clinically or röntgenologically, cancer of the supra-ampullary area from pyloric carcinoma or obstructing ulcer. Our series has refuted published traditions that jaundice is the important feature of cancer of the ampullary portion. When jaundice is present diagnosis must be made largely on the evidence afforded by Röntgen-ray methods. However, we have seen duodenal obstruction the result of other malignant processes, such as carcinoma of the head of the pancreas, carcinoma of the gall-bladder, and metastatic retroperitoneal carcinoma. Also, obstruction of the third or infra-ampullary portion has resulted from the caseating mesenteric glands in tuberculous peritonitis. On the other hand, duodenal deformity or obstruction has resulted from heavy bands, from the vessels of Wilkie, from inflammatory masses, the result of a perforating gall-bladder, and from extensive adhesions following gastro-enterostomy, or after taking down a gastro-enterostomy. These malignant and benign conditions are the more important possibilities

to bear in mind when one is confronted with an actual or apparent lesion of the duodenum other than ulcer, especially when it is associated with obstruction.

Type of Lesion.—With the exception of two large malignant papillomas all the lesions could be classified as stenosing adenocarcinomas. Nagel, in a study of three specimens obtained at necropsy, found an annular, well limited constricting duodenal carcinoma in two; one was above and one below the ampulla of Vater. In both of these cases the head of the pancreas was moderately involved. The third specimen was an indurated ulcerative carcinoma with moderate stenosis; the pancreas was also affected in this case. In one case there was local glandular involvement, but in none was there evidence of other metastasis. Microscopically the three necropsy specimens varied from a fairly well differentiated type of carcinoma with irregular acinous structures, lined by high columnar cells and interwined with connective tissue strands, to one less differentiated, showing just a few gland-like structures and marked by areas of degeneration and local infiltration with lymphocytic cells. The third represented a type about midway between these two.

CONCLUSIONS

1. Of fifteen cases of primary carcinoma of the duodenum, six were in the supra-ampullary portion, six in the ampullary, and three in the infra-ampullary.

2. Twelve of the patients were males, and the average age was fifty-six years. The duration of the disease averaged thirteen and four-tenths months.

3. The onset of symptoms was fairly abrupt in half of the patients. The pain was severe in only two, and mild or negligible in the remainder. In ten the pain or discomfort appeared from one to four hours after meals. Flatulency, pain or distress, the retention type of vomiting, dehydration, and toxæmia were the major symptoms. In most cases the course was rapidly progressive. Jaundice, except as a terminal symptom, was rare, even in the ampullary group.

4. Tumor was found in five (33.33 per cent.), and it was present only in supra-ampullary and ampullary portions.

5. In twelve of the fifteen cases in which gastric analysis was made, seven had free hydrochloric acid in subnormal amount; five had achlorhydria. Gross gastric retention was present in all except one. In the infra-ampullary group excess fluid containing bile and pancreatic juice was noted.

6. A dilated stomach with considerable barium residue without a demonstrable gastric lesion was the usual Röntgen-ray finding. In two, gastric and duodenal dilatation and barium retention made an exact anatomic diagnosis possible.

7. The toxæmia of high intestinal obstruction is a serious complication and invariably present in these cases. Diagnosis and treatment are discussed.

8. After proper pre-operative treatment a palliative gastro-enterostomy is a justifiable procedure.

9. Conditions that may give rise to difficulty in differential diagnosis are malignant and benign pyloric obstruction, carcinoma of the head of the pancreas or gall-bladder with involvement of the duodenum; carcinoma of the ampulla or terminal portion of the common duct; and benign duodenal obstruction, the result of bands when there are supra-duodenal vessel of Wilkie, inflammatory masses, peritoneal tuberculosis, and extensive post-operative adhesions.

10. The results of gross and microscopic examination of necropsied specimens are given.

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EPITHELIOMAS IN SEBACEOUS CYSTS*

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Sebaceous glands appear in the skin of the human embryo about the fifth fetal month as single, or occasionally double, buds of the hair follicles. These follicles develop as a downgrowth of cells of the stratum germinativum.[11] The distal ends of the anlage become lobulated, fatty degeneration of the central cells of the mass progresses and forms the lumen of the alveoli and ducts of the gland. The fully developed sebaceous gland is a simple or branched alveolar organ scattered through the skin of almost the entire surface of the body.[8] Probably nine-tenths of the sebaceous glands are closely associated with hairs. The duct for each gland usually opens into the sheath of a hair follicle although it may open directly on the surface of the skin. Usually only one gland is connected with a hair but there are cases in which the acini may encircle the hair completely. In certain regions, the forehead and nose for example, sebaceous glands are more concentrated than on the extremities or back. The skin of the palms and soles, and dorsum of the distal phalanges of the fingers and toes is believed by many to be free from sebaceous glands.

The secretion of the sebaceous glands is first noticed about the fourth or fifth year, reaches its maximum in adult life, and tends to disappear in old age. The lining of the duct and alveolus is flattened epithelium. The cells of the margin of the saccule multiply rapidly, and are pushed by growth of those behind into the lumen of the acinus away from nutrition. Here they undergo fatty degeneration until finally they are reduced to the granular fatty, almost cell-free material which is sebum.[9] Modified sebaceous glands are found around the eyelids (meibomian glands), mammary papillæ and areolæ of the female, glans penis and prepuce, labia minora, glans and prepuce of the clitoris.

Atheromas are now regarded as retention cysts caused by the occlusion of the duct of one or more sebaceous glands with the accumulation of the secretion. Usually no duct can be demonstrated. The flat epithelial lining of the wall can be seen and an increasing degree of degeneration of the cells adjacent to the lumen toward the centre, until the final state is noted in the fatty material and cell débris filling the cyst. Lime salts may be deposited in the sebum and, if the cyst is infected, an abscess may develop with inflammation of the adjacent tissue.

Stelwagon asserts that the favorite sites for sebaceous cysts are the scalp, face, back and scrotum. Two hundred thirty-six cases in which sebaceous cysts had been excised at the Mayo Clinic were studied. Two hundred twenty-four were simple atheromas; the remaining twelve were sebaceous cysts

* Submitted for publication, June 2, 1925.

associated with epitheliomas. The group of simple sebaceous cysts was analyzed first. Only cases of proved sebaceous cysts were chosen for the series. Very inflammatory lesions which may have been atheromas were discarded because of the possibility of error. One hundred twenty-one (54 per cent.) of the cases occurred in males, and 103 (46 per cent.) in females (Table I).

Besides the occupations tabulated there were twenty-eight others, each represented by one patient.

This scalp was the common site of the cysts. Sixty-five patients (29.01

TABLE I.

Occupation.

	Cases.	Per cent.
Attorney	5	2.23
Carpenter	3	1.33
Child	5	2.23
Clerk	4	1.78
Contractor	2	0.89
Farmer	48	21.43
Grain buyer	2	0.89
Housewife	84	37.50
Laborer	5	2.23
Mechanic	4	1.78
Merchant	6	2.68
Physician	6	2.68
Plumber	2	0.89
Railroad man	2	0.89
Realtor	3	1.33
Salesman	4	1.78
Stenographer	2	0.89
Teacher	3	1.33

per cent.) had wens in this situation. The face and neck followed in order of frequency (Figs. 1 and 2). Percentages of the number of patients in the group and of the number of lesions are given in Table II. The fact that some of the patients had multiple lesions in different regions of the body accounts for the difference in the two percentages. A fairly accurate and simple rule is that atheromas decrease in frequency from above downwards. The legs are rarely affected, and the feet practically never.

Approximately 14 per cent. of the patients with simple sebaceous cysts gave a family or personal history of malignant disease. Four patients (1.78 per cent.) had recurring lesions. Three patients (1.33 per cent.) had lesions in surgical scars; two lesions followed breast amputations, and one followed thyroidectomy. Twenty-nine patients (12.94 per cent.) had multiple lesions; twenty-two (9.82 per cent.) were in the same region of the body. For example, one patient had eight separate cysts of the scalp. Atheromas of the buttocks were invariably diagnosed lipomas by clinicians. The youngest patient of the series was aged six years. He had had two lesions of the forehead since birth. Many patients had had tumors since early childhood, and one man had had a tumor for forty-six years. The tumors varied in size from a few

TABLE II.

Site of Lesion.

	Number	Right	Left	Median line	Lesions, per cent.	Patients affected, per cent.
Abdomen	5	2		3	2.16	2.23
Arm	2	1	1		0.87	0.89
Axilla	7	3	4		3.03	3.12
Back	10		1	9	4.32	4.46
Breast	13	1	12		5.62	5.80
Buttock	8	3	5		3.46	3.57
Cheek	22	12	10		9.51	9.82
Chest	10	4	5	1	4.32	4.46
Ear	1	1			0.43	0.44
Face, including forehead, cheeks, jaw, lips and parotic region	37	21	15	1	16.01	16.51
Fingers	3	1	2		1.29	1.33
Forehead	7	1	5	1	3.03	3.12
Hand (palm)	3	3			2.59	2.67
Hand (dorsum)	3	2	1			
Jaw	3	3			1.29	1.33
Leg	1		1		0.43	0.44
Lip (lower)	1	1			0.43	0.44
Lumbar region	2		2		0.87	0.89
Mastoid region	3		3		1.29	0.89
Neck, including back and front	34	12	9	13	14.71	14.73
Parotid region	4	4			1.73	1.78
Scalp	65				28.13	27.67
Scrotum	2				0.87	0.89
Shoulder	11	5	6		4.76	4.02
Thorax, including front and back of chest and breasts	33	5	17	11	14.28	14.72
Temporal	5	5			2.16	2.23
Thigh	6	6			2.59	2.67

millimeters to 6 cm. in diameter. The atheromas developing in the palm deserve mention, for it is generally supposed that there are no sebaceous glands in this situation. The feet and legs were, with one exception, free from atheromas.

Epitheliomas arising in sebaceous cysts have been described by Ricker and Schwalbe, Seff and Berkowitz, and Busfield. Ricker and Schwalbe reviewed the literature up to 1914, and found that forty-three cases of malignant change in atheromas had been reported; these they embodied in their study. In this group there were twenty-two males, sixteen females, and in five cases the sex was not mentioned. Seventeen patients had ulcerated lesions. The lesions predominated in the face, eight were of the meibomian glands of the eyelids, three of the forehead, six of the cheeks, seven of the nose, one of the inner angle of the eye, and seven of the scalp. One patient was aged less than twenty; ten were sixty or

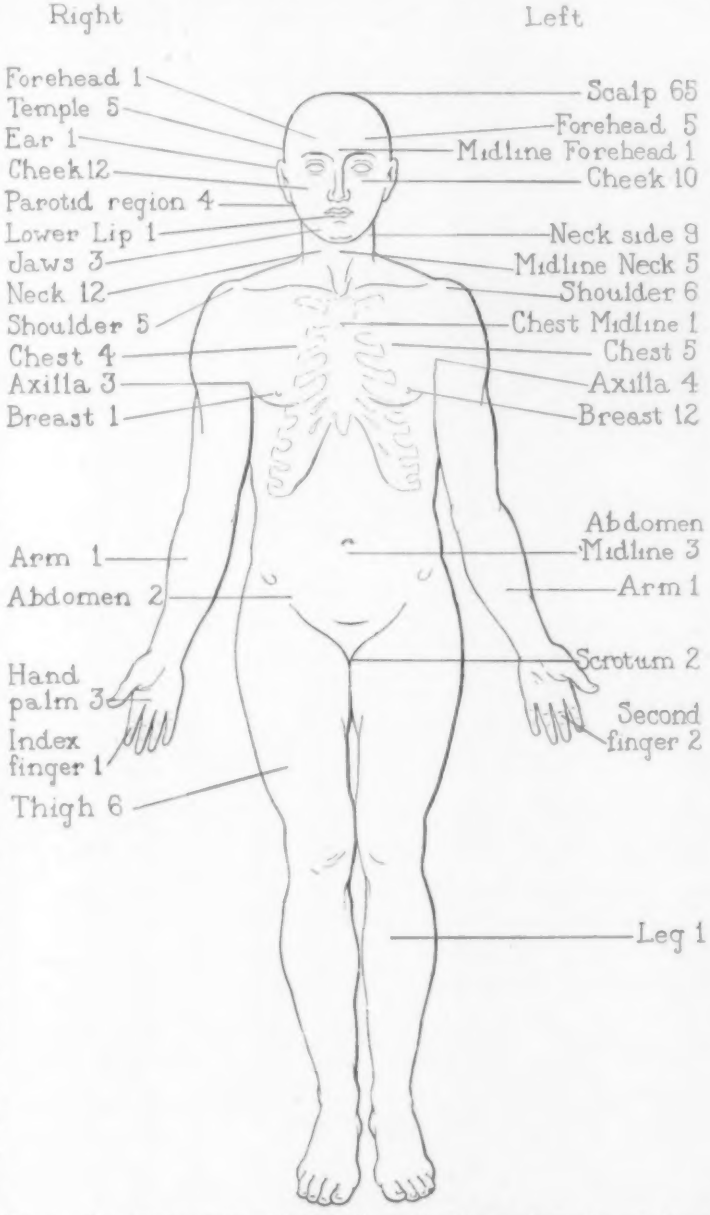

FIG. 1.—The anterior aspect of the body illustrating the number and approximate location of the sebaceous cysts.

more. The tumors usually grew slowly and their size varied from 3 to 10 cm. in diameter.

Seff and Berkowitz, in 1916 reported three cases of epitheliomas developing from sebaceous cysts. Their patients were aged twenty-seven, forty-seven, and fifty-one, respectively. The cysts varied in size from 1.5 to 2.5 cm. in diameter. All of the lesions occurred on the head. One, the only fatal case, developed in a recurring cyst of the scalp; one was of the forehead, and one of the temple. Local injury seemed to be a factor in the production of the malignant change. Heredity was not a factor in their series. Two of the tumors were squamous-cell epitheliomas, and one a basal-cell epithelioma. One lesion was an infected ulcerated cyst.

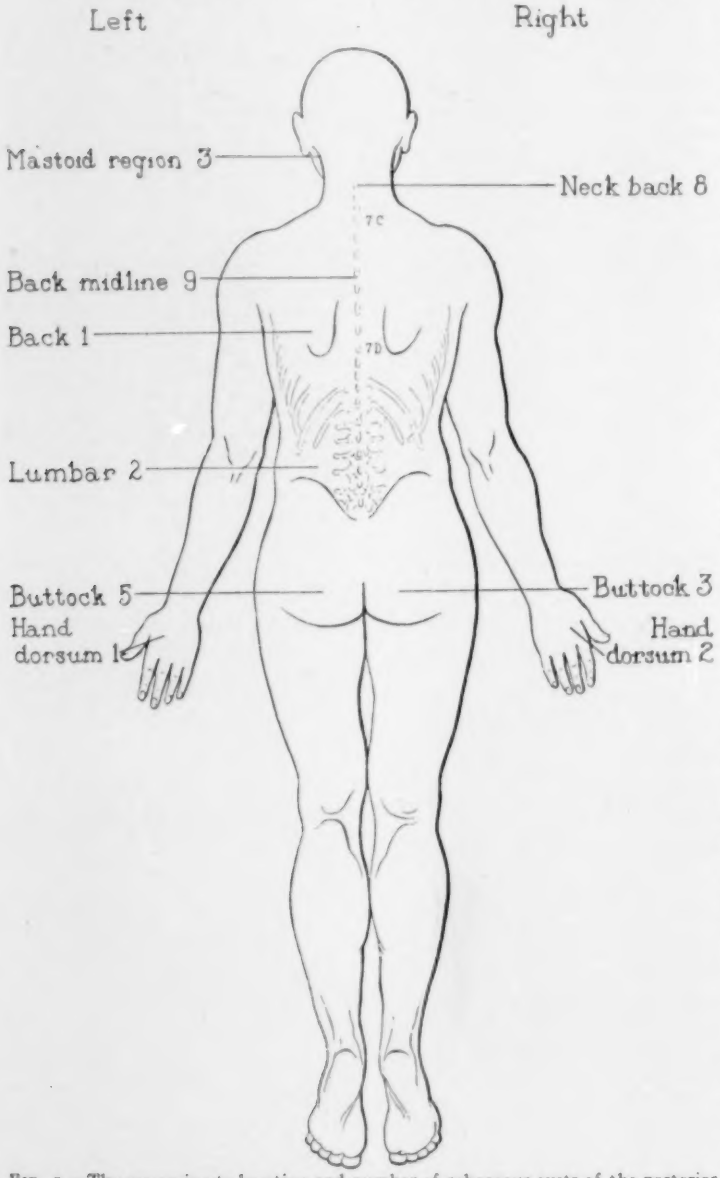

FIG. 2.—The approximate location and number of sebaceous cysts of the posterior aspect of the body.

Busfield reported a case of a rodent ulcer developing from a sebaceous cyst of the temple. Narat has recently described a case of an epithelioma developing on the surface of an ulcerated sebaceous cyst of the scalp.

Twelve cases of epithelioma developing in sebaceous cysts were studied

in the present series.† Eight of the tumors were observed simultaneously with 224 simple sebaceous cysts, so that the approximate incidence of malignancy in this group was 3.44 per cent.‡ In a few cases it was necessary to depend on the history given by the patient or attending physician for the diagnosis of atheroma because the malignant condition so overshadowed the microscopic picture that only the neoplasm could be accurately observed and described. The tumors in this group, arranged according to MacCarty's classification, are textoblastomas and pseudotextomas.[13, 14] Textoblastomas are those malignant neoplasms, "which are composed of cells so undifferentiated that it is impossible positively to recognize the textocytes (adult tissue cells) into which they would develop if differentiation occurred;" these tumors are called sarcomas, carcinosarcomas, and so forth. Only one case (Case XII) was in this group. The remainder of the new growths in this series are grouped with the pseudotextomas, which include those malignant tumors composed of partly differentiated cells, and resembling somewhat normal adult tissue cells of the organism. In this group are adenocarcinomas, sarcomas, and most epitheliomas.

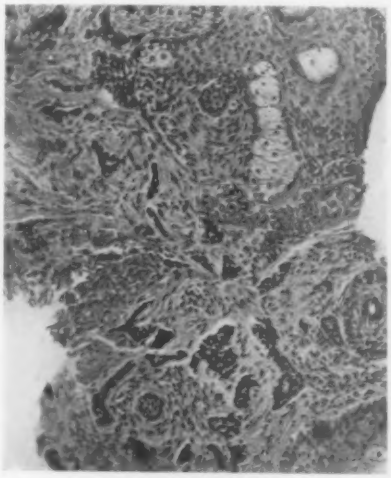

FIG. 3.—Basal-cell epithelioma (Case I). (x 75.)

FIG. 4.—Squamous-cell epithelioma, grade 1, showing marked differentiation (keratinization) in more than 75 per cent. of the section (Case IV). (x 35.)

REPORT OF CASES

CASE I.—A farmer, aged forty-two, complained of a "sore" and later a "lump" of the nose present for five years. With local treatment this tumor ulcerated and discharged thick material. The father of the patient had cancer of the face and an aunt had cancer of the arms. Examination of the tissue removed at operation revealed basal-cell epithelioma apparently arising in a sebaceous cyst (Fig. 3). The ultimate result of this case is unknown.

CASE II.—A drayman, aged forty-five, complained of a tumor of the left cheek present for twelve years. The lesion had ulcerated at intervals. Three years after the

† Since this report one patient with an epithelioma in an atheroma of the scalp and one of the side of the neck have been examined.

‡ This percentage is probably higher than would be found in some series because not all sebaceous cysts removed were sent to the laboratory for examination, and because highly inflammable lesions in the skin which may have been sebaceous cysts were disregarded in selecting cases.

growth was noticed, it was removed and diagnosed a sebaceous cyst; it recurred within three years. Nine years after the recurrence, a second cyst was excised, and was diagnosed a basal-cell epithelioma arising in an atheroma. Three years after the second operation this patient had a recurring lesion of the left cheek.

CASE III.—A woman, aged sixty-one, came to the clinic because of a prolapsed uterus. During the examination a cystic tumor about 2 cm. in diameter was discovered just beneath the skin of the left shoulder blade. The patient did not know how long this nodule had been present. Her father had had a malignant growth removed from his lip. The cyst was excised and found to be an atheroma containing squamous-cell epithelioma, grade 1. The final result in this case is not known.

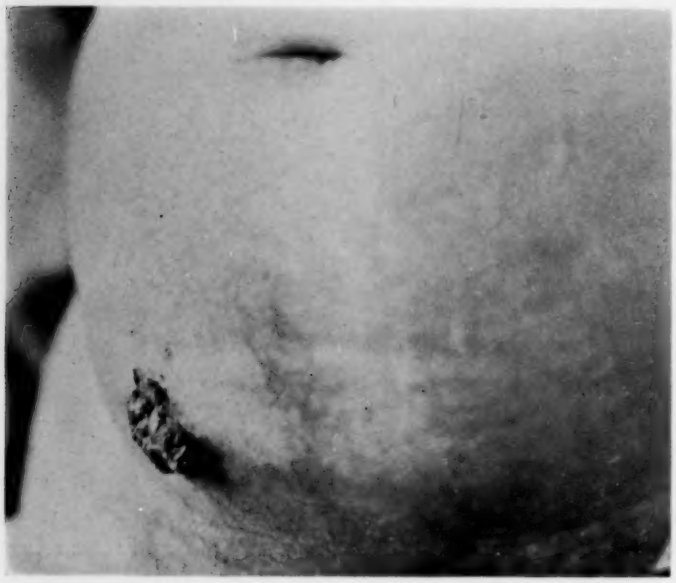

FIG. 5.—The gross appearance of the lesion at the time of examination (Case VI).

CASE IV.—A woman, aged seventy-five, came to the clinic because of a recurring cyst of the scalp. The growth was removed and found to be a wen. Two years later the tumor recurred and was again excised. The tissue removed at the second operation was found to be squamous-cell epithelioma, grade 1, in a sebaceous cyst (Fig. 4). The patient lived three years and eight months after her last operation without recurrence, then died from old age.

CASE V.—A man, aged fifty-eight, had had a cyst of the right occipital region for ten years. It had been opened and had drained "pus and cheesy material" at intervals for years. The lesion was removed and proved to be a sebaceous cyst 2.5 cm. in diameter containing squamous-cell epithelioma, grade 1, which had differentiated markedly. Nothing definite is known concerning the outcome in this case.

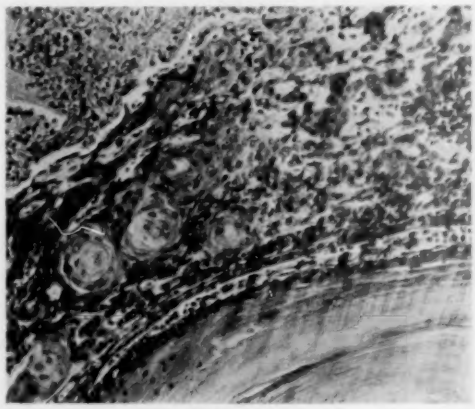

FIG. 6.—Squamous-cell epithelioma, grade 1. The edge of an epithelial pearl is shown with complete differentiation of the cells into keratin (Case VI). (x 80.)

CASE VI.—A man, aged forty-nine, came to the clinic because of urinary disturbances and an ulcerating sore of the abdominal wall that would not heal (Fig. 5). The lesion had appeared about one year before as a small "boil" or "pimple" near McBurney's point. After violent squeezing on several occasions cheesy material extruded. The lesion never completely healed. It would drain, scab over, and then break down.

The tumor gradually increased in size; when the patient was examined it was about 3 cm. in its greatest dimension. It was excised and found to be squamous-cell epithelioma, grade 1, arising in a sebaceous cyst (Fig. 6). There had been no recurrence two months after the operation.

CASE VII.—A woman, aged fifty-six, had had a "growth" on her right cheek for twelve years. Her father and one cousin had died from cancer. Two years before, a sebaceous cyst had been diagnosed. It was removed, promptly recurred and was excised a second time. At the Mayo Clinic a cystic tumor 1.5 cm. in diameter was removed and diagnosed atypical squamous-cell epithelioma, grade 2 (Fig. 7), apparently arising in a sebaceous cyst. Eight years and one month after operation there had been no recurrence.

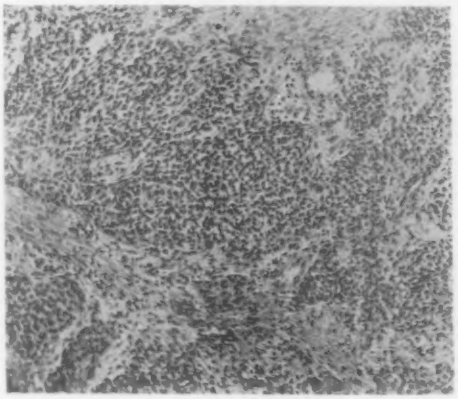

FIG. 7.—Atypical squamous-cell epithelioma, grade 2 (Case VII). (x 60.)

CASE VIII.—A woman, aged sixty-five, had been troubled with a recurring atheroma of the left cheek for seventeen years. The tumor had been removed twice before the patient came to the Mayo Clinic, the last time seven years previously. At the examination a painless, slightly ulcerated cyst of the right cheek, about 0.5 cm. in diameter, was found. Under local anæsthesia the diseased tissue was excised. Microscopic examination revealed a prickle-cell type of epithelioma, grade 2, arising in an atheroma (Fig. 8). This woman was well without recurrence twelve years and one month after her last operation.

CASE IX.—A man, aged forty-four, came desiring advice and treatment concerning a tumor of the front of his left leg just below the knee. This nodule had been present for five years and had slowly increased in size until at the time of the examination it was about 2 cm. across. It had never been painful. Under local anæsthesia the growth was removed and found to be a sebaceous cyst containing in its lumen a prickle-cell type of epithelioma, grade 2. There was no recurrence three months after removal of the tumor.

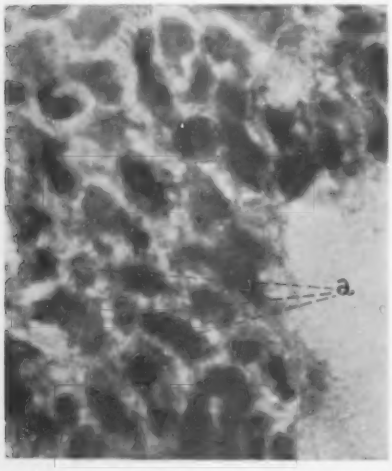

FIG. 8.—Prickle-cell epithelioma, grade 2; high magnification to show the "prickles" between the cells at *a* (Case VIII). (x 1200.)

CASE X.—A man, aged eighty-two, had noticed a "pimple" on his left temple for five months before coming to the clinic. This lesion had increased rapidly in size until, at the time of admission, it was about 1.5 cm. in its greatest dimension. The tissue removed was a squamous-cell epithelioma 2, arising in a sebaceous cyst (Fig. 9). This man died from apoplexy eleven months after operation.

CASE XI.—A man, aged thirty-eight, had had a gradually enlarging "lump" on the back of his head since childhood. An aunt had died from cancer of the breast. Three times, in the three months just preceding the patient's visit to the clinic, this cyst had been removed but had recurred. At the clinic a wide excision was performed, and squamous-cell epithelioma, grade 3, was found in an atheromatous cyst. There were many mitotic figures in the malignant cells (Fig. 10). This man was alive and well eight years after operation.

CASE XII.—A woman, aged seventy-one, had had a cystic tumor of the right cheek for twenty years. Three years after it first appeared it was excised, but it soon recurred. Both her grandfathers had died from cancer. The tumor remained about 0.5 cm. in diameter until three months before examination at the clinic, when it began to enlarge rapidly. The patient lost 15 pounds in eight weeks. The lesion was an indurated ulcerating area strongly suggestive clinically of malignancy. A piece of tissue, 3 by 3 by 2 cm., was excised, and examination revealed squamous-cell epithelioma, grade 4, apparently arising in a sebaceous cyst. This woman died seven months after operation from carcinomatosis (Fig. 11).

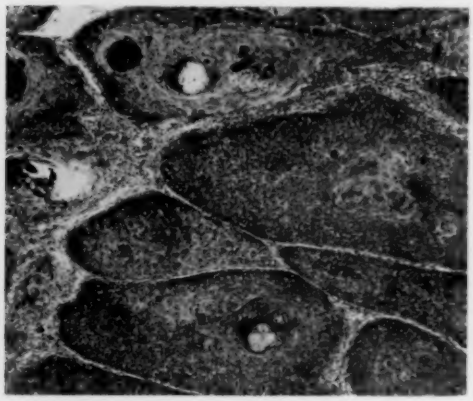

FIG. 9.—Squamous-cell epithelioma, grade 2 (Case X). (x 35.)

Seven patients (58.33 per cent.) in this group of twelve cases gave a family history of malignant disease. The lesions were about equally divided between the sexes, seven being in males and five in females. The age ranged from thirty-eight to eighty-two years. One patient was in the fourth decade and one in the ninth, two each in the sixth, seventh, and eighth decades, and four in the fifth. Three of the lesions occurred on the scalp, one on the temple, four on the cheeks, one in the nose, one on the shoulder, and one on the abdominal wall, and one on the leg (Fig. 12). Four cysts (one-third of the total) had ulcerated. The ulceration was apparently caused by abrasions from combing the hair, rubbing of clothing or by local applications used for treatment.† In most cases there was no history of recent enlargement of the lesion. One growth developed, according to the history, in five months. One fatal case (Case XII) was that of a recurring cyst of twenty years' duration (Table III).

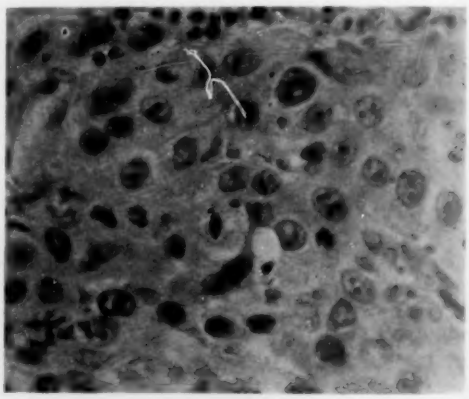

FIG. 10.—Squamous-cell epithelioma, grade 3. Large malignant cells showing little differentiation, many containing mitotic figures (Case XI). (x 350.)

If the contour of the cyst was preserved the epithelioma could be distinguished grossly as a flat or papillary gray to white firm area growing from the wall into the lumen and apparently later invading adjacent structures. Ten of the epitheliomas were the squamous-cell type and two basal-cell type.[1] The squamous-cell tumors, classified according to the method first described by Broders,[2, 3] were: four epitheliomas grade 1, four

† Kaufmann mentioned an epithelioma developing in an atheroma and observed that ulceration usually came on before the malignant condition was noticed.

epitheliomas grade 2, one epithelioma grade 3, and one epithelioma grade 4. Two prickle-cell tumors were included in this series. They were both graded 2. The prickle cells are usually most readily found close to the blood-vessels where the malignant cells sometimes assume radial arrangement. Under high

TABLE III.
Clinical Notes.

Case	Age, years	Epithelioma	Site	Comment
1	42	Basal-cell	Nose	Father and Aunt died from cancer. Lesion on face ulcerated, nothing known regarding ultimate result.
2	45	Basal-cell	Left cheek	Recurring lesion of cheek. Lesion recurred three years after removal.
3	61	Squamous-cell 1	Left shoulder	Father had cancer of lip. No report from patient regarding present condition.
4	75	Squamous-cell 1	Scalp	Recurring lesion of scalp.
5	58	Squamous-cell 1	Scalp	No report from patient regarding present condition.
6	49	Squamous-cell 1	Abdominal wall	Infected ulcerated lesion of abdominal wall.
7	56	Squamous-cell 2, atypical	Right cheek	Father and one cousin died from cancer. Recurring lesion of cheek. Patient alive and well without recurrence eight years after last operation.
8	65	Squamous-cell 2, prickle-cell type	Left cheek	Recurring cyst of cheek. No recurrence seven years and seven months after excision.
9	44	Squamous-cell 2, prickle-cell type	Left knee	No trouble three months after operation.
10	82	Squamous-cell 2	Left temple	Lesion noticed first, five months before. Died from apoplexy one year after operation.
11	38	Squamous-cell 3	Scalp	Aunt died from cancer. Lesion recurred three times in three months. Alive and well eight years after removal with no recurrence.
12	71	Squamous-cell 4	Right cheek	Both grandfathers died from cancer. Recurring lesion of right cheek. Died from carcinomatosis seven months after operation.

magnification, with the condensor aperture of the microscope very small, the prickles between the cells can be demonstrated. In some areas these tumors resemble the basal-cell type of epitheliomas. Broders [5] says that he has never seen an epithelioma of the prickle-cell type that spread by metastasis, although from the appearance of the lesions there is nothing to account for this peculiarity. Careful examination of the sections of epitheliomas 1, reveals marked

keratinization of the cells. The differentiation varies in this group from almost complete to approximately 75 per cent. The most highly differentiated squamous epithelium in a tumor is completely keratinized, as is seen in epithelial pearls.[4] But in grading one must not depend only on the formation of epithelial pearls. There are all grades of keratinization of squamous-cell tumors from the slightest to the most extensive deposits in the cytoplasm. An epithelioma graded 3 may contain pearls and the remainder of a section of the tumor be composed of undifferentiated highly malignant cells (Fig. 10). In epitheliomas graded 2, the differentiation includes from 75 to 50 per cent. of the tissue in the sections (Fig. 9). In Case VII the lesion was an atypical squamous-cell epithelioma (Fig. 7). The nuclei of the cells were not so chromaphilic as in ordinary flat-cell carcinoma. There was no typical formation of epithelial pearls. The cells of the tumor had lost their usual alveolar arrangement and were scattered with their long axes pointing in many directions rather than in concentric circles, as is seen around pearls, or in more or less regular strata. The tumor cells were more rounded than was common in squamous-cell carcinoma, and the usual pavement-stone-like cells were for the most part absent. In some areas the tumor suggested a basal-cell type, but more careful study showed it to be composed of atypical squamous cells.

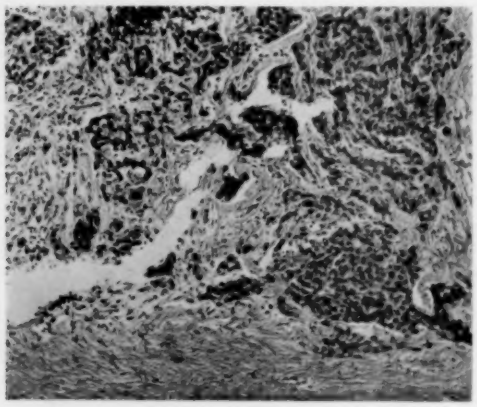

FIG. 11.—Squamous-cell epithelioma, grade 4, composed of large undifferentiated malignant cells containing no appreciable keratin (Case XII). (x 60.)

The epithelioma graded 3 showed approximately 30 per cent. of differentiated areas. The tumor cells were large and contained hyperchromatic nuclei. There were many mitotic figures. The clinical history of rapid recurrences following partial removal of the tumor in this case was exactly in line with the microscopic picture.

The epithelioma graded 4 was composed of large, apparently rapidly growing cells without cornification. The nuclei of the cells were unusually large. MacCarty [12] has pointed out that with such cells in lymph-nodes it is almost impossible to tell the exact type of neoplasm from which they arose. The extreme malignancy in this case was shown by the death of the patient, within seven months, from generalized metastasis.

CONCLUSIONS

Sebaceous cysts can develop in almost any portion of the body covered by epidermis, the palms included. They are retention cysts caused apparently by obstruction of the duct of the gland and accumulation of the sebum. All sebaceous cysts should be removed, for they may become the site of a malig-

nant tumor. Approximately 3.44 per cent. of the sebaceous cysts in this series eventually became malignant. The lesion should be excised if it is ulcerated, and excision is imperative if the lesion recurs. Obviously all sebaceous cysts should be examined carefully for malignant change. Heredity was apparently an etiologic factor in the development of epitheliomas in the cysts studied, since 58.33 per cent. of the patients with epitheliomas gave a family history of malignancy, while only 13.83 per cent. of the patients with simple uncomplicated sebaceous cysts gave a personal or family history of malignancy. Local irritation, while it may be an item in causing the development of malignant change, was not most important factor.

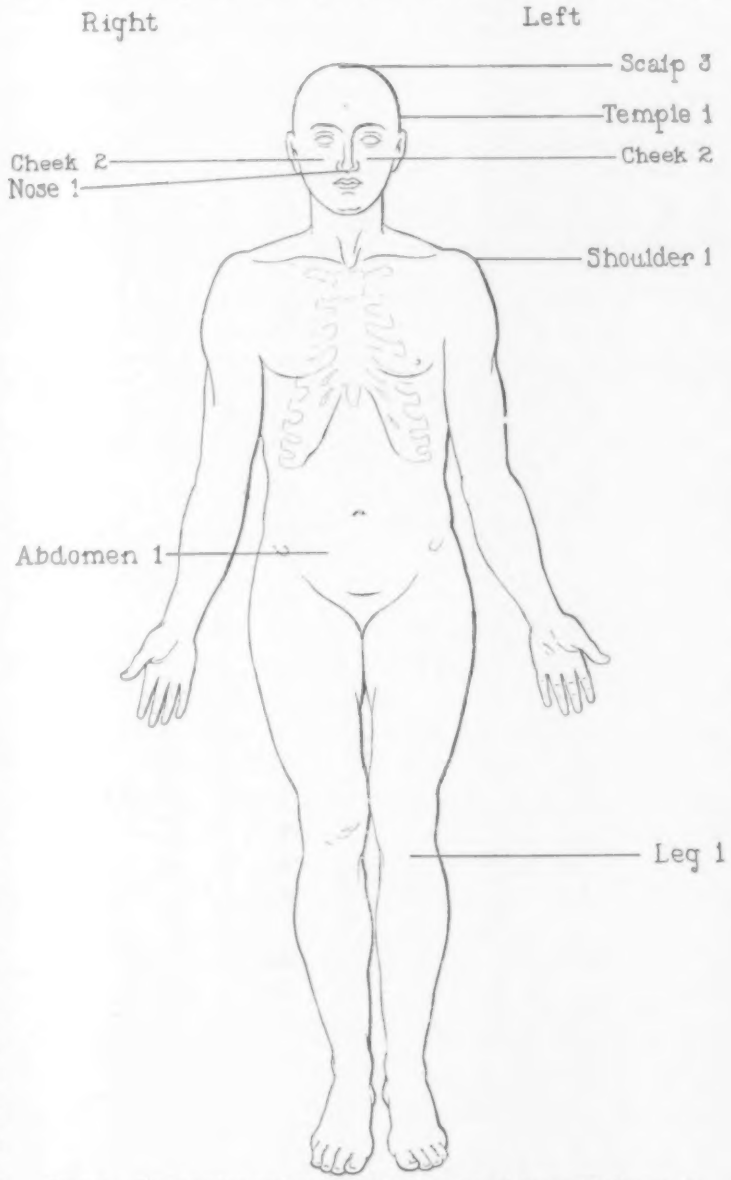

FIG. 12.—The number and approximate location of the epitheliomas in sebaceous cysts.

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CARCINOMA OF RECTUM*

REPORT OF OPERATIONS AND PRESENTATION OF CASES

By Joseph A. Blake, M.D.
of New York, N.Y.

The cases embodied in this report were operated upon between the years 1906 and 1912 in the Roosevelt and Presbyterian Hospitals. They comprise all of those of which I have been able to find records. I regret that the follow-up in these cases has been so meagre as to make it impossible to state the average duration of life after operation, and thus compare the results of the different operations. The number of operations is also too few to enable one to deduce much from them.

Of sixteen operations ten were combined operations with excision of the lower sigmoid and entire rectum in one stage, with simultaneous formation of an inguinal colostomy. There was no operative mortality in this group. Of these, two are alive, one seventeen the other sixteen years after operation (both presented); one lived twelve and one-half years and is said to have died of recurrence; one died of recurrence in five years and two months; in one other case I was unable to remove the growth and she died in six months. The other five have been lost sight of.

There were six combined operations in which a low anastomosis with preservation of the sphincter was performed. Of those six, there was one post-operative death on the tenth day from pulmonary embolism; the others recovered from the operation. One of these is alive and well fourteen years after operation and has recently taken out a large life insurance. He was under thirty years when operated on. One had a stricture and died of recurrence two years after operation. The other two have been lost from observation.

One patient was operated by the combined method with complete removal of the rectum and anus with the formation of a perineal colostomy. She died on the fourth day from low intestinal obstruction, as proved by autopsy, a few hours after a secondary inguinal colostomy. Of the total 16 cases, there was thus an operative mortality of two, that is, 12½ per cent. Three can be considered as cures, being alive and well from fourteen to seventeen years after operation. There may be others still alive, but we have been unable to reach them.

There were three accidents in the group of combined operations with inguinal colostomy. In one a loop of small intestine herniated between the sutures in the pelvic floor, but the obstruction was recognized and relieved

* Presented at a joint meeting of the New York Surgical Society and of the Philadelphia Academy of Surgery, held February 11, 1925.

by secondary celiotomy on the third day with uneventful recovery. An ureter was injured in each of two women; in one an anastomosis was immediately done successfully; in the other a persistent urinary fistula resulted.

In regard to the choice of operation for carcinoma, I believe that nearly all surgeons are convinced that the combined abdomino-perineal is the only rational one, and it is needless for me to review the reasons wherefor. They have been very ably stated by Dr. D. F. Jones and proven correct by his results. The only question for discussion being, perhaps, the methods by which the operations should be performed. The cases may be divided into two groups, one in which the growth is low and in which the preservation of the sphincter ani entails a risk of ineffectual removal. For this group the entire rectum and anal region should be removed and an inguinal colostomy instituted. The other group comprises those cases in which the growth is high and in which there may not be a downward spread to the lymphatics of the perineum, anus and ichio-rectal regions. I say "may not," for there is always a question of doubt. Unquestionably in these higher growths the operation offering the best chance of immunity from recurrence is complete excision and inguinal colostomy, but in the face of strenuous opposition to an inguinal colostomy one is justified perhaps, if all concerned understand the risk, in preserving the sphincter and doing a low anastomosis. The one in my series who has had no recurrence fourteen years after the operation, in whom this low anastomosis was done, had a relatively high growth just reached by the examining finger. I feel that complete extirpation and inguinal colostomy is the best operation for all cases and the only permissible one for low growths and I have refused to operate on such cases unless they permitted me to do it.

In regard to the operative mortality of the combined abdomino-perineal operation, all my operations have been done in one stage; that is, the colostomy has been done and the rectum removed at the one operation. There have been more than ten of these operations, as I reported fourteen in 1911, and there have been a few since then. The last case I operated died, a woman of seventy-five years. All the others recovered from the operation. The operation is a shocking one, but a clean one, and convalescence is rapid. To perform it properly, there should be three assistants, one at least of whom should be an experienced operator, and the team work must be good.

As I have done it, a sufficiently long median incision is made; the operability determined; the site of division of the intestine selected, and then a split muscle (McBurney incision) made through the left lateral abdominal muscles. Through this incision a long clamp is introduced and the gut strongly clamped at the point of division. Another small clamp is placed just below this and the gut divided with the cautery, and the proximal end pulled out through the lateral incision, thus completing the colostomy, no suture being necessary. The pelvis is then dissected as usual, freeing the gut as low as possible. The

patient is then put in the lithotomy position and the operator completes the perineal dissection while the first assistant closes the floor of the pelvis and the abdominal wound. The perineal wound is closed, and a stab drainage wound made alongside the sacrum for a fair-sized drainage tube.

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TRANSACTIONS

OF THE

NEW YORK SURGICAL SOCIETY

AND OF THE

PHILADELPHIA ACADEMY OF SURGERY

Joint Meeting Held February 25, 1925

DR. EUGENE H. POOL in the Chair

SYMPTOMS AND LATE RESULTS IN NEOPLASMS OF THE SPINAL CORD

DR. CHARLES A. ELSBERG read a paper with the above title, for which see p. 1057, ANNALS OF SURGERY, vol. lxxxi.

In illustration of his paper Doctor Elsberg presented a number of patients as follows:

CASE I.—A young man upon whom he had twice operated for an extramedullary spinal cord tumor at the sixth cervical segment. A well-encapsulated tumor was removed which was reported by the laboratory as a fibroma. Two years later he returned to the hospital with a recurrence of his symptoms and at the second operation, performed in 1921, a second well-encapsulated growth, together with a small piece of dura, was removed. Convalescence from the second operation was satisfactory, and the report from the laboratory was that the tumor was a spindle-cell sarcoma.

CASE II.—A man from whom he had removed an extramedullary leiomyoma at the second and third cervical segments. When he was admitted to the Neurological Institute, the symptoms and signs pointed to a tumor at the second cervical segment. At the laminectomy an extramedullary tumor was removed from the level of the second cervical segment. It had a process extending through the dura and through an intervertebral foramen. The tumor was a leiomyoma which contained a large number of blood-vessels. Improvement was noted by the patient as soon as he awoke from the anæsthesia and there was a steady and rapid return of power in all four limbs. He has completely recovered.

CASE III.—A patient from whom he had removed an extramedullary spinal cord tumor from the level of the seventh segment in 1921. The tumor lay in front of the cord and had caused a slightly marked spastic paraplegia with sensory disturbances that were more like those of a growth within the substance of the cord. The patient suffered also from gastric distress after meals and on account of the gastric symptoms had been operated upon in another institution for suspected gastric ulcer which was not found. This patient demonstrated that abdominal symptoms of spinal root origin may be mistaken for symptoms of intra-abdominal disease.

CASE IV.—A woman, twenty-five years of age, from whom in 1923 he had removed an extramedullary tumor from the left and posterior surface of the cord at the eleventh to twelfth thoracic segments. The patient had a positive Wassermann reaction and gave a five months' history of numbness in the toes of the left foot which had gradually spread up to the left leg. Ten

weeks before the operation the right limb became affected and soon walking became impossible.

Upon physical examination, it was found that the left lower extremity was weaker than the right. There were marked sensory disturbances which involved dermatoes only up to the fifth lumbar, and muscle and joint senses were markedly impaired in the lower limbs.

The unusual features of the case were the rapid onset of the symptoms in the presence of a positive Wassermann reaction and the very rapid return of function after the removal of the tumor, so that within a few weeks all of her motor and sensory disturbances had disappeared.

CASE V.—A woman, with a history of four years' duration, from whom he had removed an extramedullary tumor from in front of the cord at the level of the fourth cervical segment. The physical signs presented by the patient were mostly those of a right hæmiparesis, and it was of interest that tactile sensibility was normal all over the body, while pain and temperature sensibility were only slightly disturbed. The manometric tests failed to show any distinct interference with the circulation of spinal fluid. The patient recovered satisfactorily from the operation and left the hospital twenty days after the surgical interference. She has steadily improved since that time.

DR. JAMES H. KENYON presented a woman, thirty years of age, whose symptoms began in 1922 with pain in both shoulders, but mostly in the left. A few months later the legs seemed to be weaker, the pain had extended down the left side, also across the lower abdomen, and there were various sensations of heat or of pins and needles in the soles of the feet, particularly the right.

By October, 1923, about one and a half years after the onset, she could not walk at all, had a tight band-like sensation at the nipple line, breasts were very tender, so that she could scarcely touch them. Breathing became difficult and a deep-seated pain appeared in the centre of the chest. Two months later she could not stand, could scarcely sit up, and was uncomfortable all the time. Urination became frequent and scanty and the bladder never felt empty.

March 14, 1924, she entered the Neurological Institute; unable to stand or walk, could not even sit up, could not pass any urine, had to be catheterized. The band-like sensation around the nipple line was worse, paræsthesia of legs and feet more pronounced, especially on the right side.

With a diagnosis of tumor of the spinal cord, extra-medullary, but inside the dura at the level of first thoracic vertebra, on March 29, 1924, he removed the spines and laminæ of the seventh cervical and first thoracic vertebræ. Color and contour of dura normal, rather tight, no pulsation. Some increased resistance felt on palpating dura under the seventh lamina. Dura opened, very little fluid, tumor exposed, an elliptical incision in the adherent dura overlying it was made. By slight traction on this piece of dura and gentle manipulation with a separator the tumor was easily removed without any trauma to the cord. During this manipulation the usual amount of clear fluid escaped, showing that there had been a partial block of the spinal canal. The tumor was molded around the posterior surface of the cord at the level of the lamina of the seventh cervical vertebra. It measured 2.5 by 2 by 0.5 cm.; it was not adherent to the cord or nerve roots.

Pathological Examination.—Endothelioma.

Post-operative Course.—The patient could move her legs on the third day; was out of bed on the twelfth day and on the thirteenth day walked the length of the hall, something she had not done for five months. She left the hospital on the twenty-eighth day. At the present moment, February 25, 1925, the patient is normal in every way; all tests are normal. She walks perfectly. The bladder function is all right.

Dr. Charles H. Frazier (Philadelphia) reviewed the last forty cases of presumptive spinal cord tumors, covering his experience in the last few years, in which a laminectomy had been performed. He regarded the most difficult problem in spinal cord tumors to be the diagnosis rather than the localization, differing in this respect from brain tumors in which the reverse is true. One learns more, perhaps, from reviewing one's mistakes than displaying one's successes, so the speaker had selected the eight of these forty cases in which he had failed to find a tumor, cases in which the diagnosis had been inaccurate. These cases proved to be multiple sclerosis, amyoptrophic lateral sclerosis, transverse myelitis and various syphilitic lesions.

These diagnoses had been confirmed by the subsequent course of events and by the development of symptoms not apparent before the laminectomy was performed. Of these eight cases in which a mistake in the diagnosis had been made, six had been referred to him by competent neurologists as spinal cord tumors.

In the matter of diagnosis, Doctor Frazier thought it perhaps not so important what these eight cases presented as what they did not present. In these failures there was in none a typical tumor history and especially notable was the absence of pain. In the majority of cases, in 90 per cent. of his own series of verified spinal cord tumors, there was a definite, typical spinal cord tumor history, that begins with pain and months' duration, sometimes years, and always and continuously referred to the same region. Pain is the most important and essential feature not only in the diagnosis, but often in the localization of spinal cord tumors. As they begin with pain, there follow paræsthesias and almost always after these the motor disturbances, atrophies, paresis or paralyses. *In only 10 per cent. of his series was there a painless history* and in every one of these the tumor proved to be extradural. These percentages may differ from those of Doctor Elsberg's series; if so, this can be explained by the difference in the point of origin of the tumors.

In the majority of mistaken diagnoses difficulty was experienced in the attempted segmental localization. In the verified tumor there is invariably one or more of the following suggestive features; a precise sensory level, definite pain distribution, sympathetic phenomena, loss of a single reflex, muscle atrophy, involvement of the diaphragm. Except in lesions of the cauda equina the pelvic viscera were not involved until comparatively late. One of the outstanding points in differential diagnosis is this; the findings must be definite, not vague; they should be clear cut, not difficult of interpretation. He usually found when he had made a mistake that the history was atypical, the physical findings were not sharp and clearly defined. In one of his series which proved later to be a case of multiple sclerosis, the objective symptoms were vague and the history by no means typical. In one case of amyotrophic lateral sclerosis, while the early history was suggestive, there was no well-defined sensory level. In one case of transverse myelitis the course was rapid, pain was not a prominent factor, incontinence developed

early. Hind sight is better than foresight, but the true nature of the lesion did not reveal itself in these mistaken diagnoses until some time after the exploration.

Too much emphasis, the speaker thought, had been laid upon the presence of a spinal block. It is not a matter of vital importance. It is gratifying of course to know if the patient has a spinal block, but one's judgment should not be overinfluenced by it. If in cases without evidence of spinal block an exploratory laminectomy is not performed, many tumors will be overlooked, and per contra there may be cases of spinal block in which the block is not due to tumor, but to some other lesion, a pachmeningitis or a meningomyelitis. For these reasons one should place a reservation on the importance of spinal block.

Among the verified tumors there was only one in which the tumor was not uncovered at the first operation; in this case the segmental localization was higher than the lesion. As a rule, if an error has been made the lesion is higher rather than lower than the anticipated level, and it becomes necessary to remove one or two laminæ above the contemplated exposure, but in this case the reverse was the case. Eleven per cent. were extra-dural; in one the tumor was both intra-spinal and intra-cranial; in 10 per cent. the tumor was intramedullary and in 4 per cent. caudal.

As to the end results of operation: In two of the speaker's series in which the tumor was found and removed, there was no recovery of function, the duration of the lesion being two and six years. In all but these two there was recovery of function both motor and sensory and the patients became ambulant. In some cases recovery of function is surprisingly slow, when the disturbance of function must be the result of pressure and not of degeneration. In only one case was there a recurrence. An average of twenty-three months had elapsed before the tumor was removed.

The chief and foremost concern, therefore, in tumors of the spinal cord is diagnosis and segmental localization. The tumors are of such a character that they present few if any technical difficulties, except when they have gotten beyond the confines of the spinal canal. Perhaps the most important point to be emphasized is the excision of that portion of the spinal membranes from which the tumor takes its origin.

Dr. J. Stewart Rodman (Philadelphia) said as to the matter of pain, this is one symptom that could be relied on more than others in the diagnosis of spinal cord lesions. However, it may be absent at times, and it may not always be characteristic, and so, therefore, it may lead one astray, except in the presence of other pathognomonic symptoms. The presence or absence of pain has much to do with pressure on the posterior roots. He had been disappointed after removing extra-medullary tumors and then having the symptoms of spinal cord pressure continue. How long it takes for irreparable spinal cord damage to come about he did not know. He recently operated on a case of fibro-lipoma beautifully located by neurological findings of lipiodal, but post-operatively the symptoms continued and the patient is no

better now than before the operation. He emphasized, again, that one should look to the early neurological diagnosis as still being the most reliable diagnostic help in tumors of the spinal cord.

Doctor Elsberg, in closing the discussion, said that of course errors in diagnosis were being made, tumors not being found as expected, but this much could be said, namely, that the knowledge gained from lumbar puncture and the manometric tests had been of no little help in these doubtful cases which he classed as B or C. Class A are the typical cases; Class B not so much so, and Class C includes those which are probably not tumors. In Class B the manometric tests have helped in the correct diagnosis of not a few cases. Where spinal block exists, it may be caused by a number of different diseases, and in the group of doubtful cases undoubtedly the manometric test will help one in a certain proportion of cases to gain an increased amount of information.

CARCINOMA OF RECTUM. REPORT OF OPERATIONS AND PRESENTATION OF CASES

Dr. Joseph A. Blake (New York) read a paper with the above title, for which see p. 177, Annals of Surgery, vol. lxxxii.

Dr. Charles H. Peck (New York) presented two cases, one well after seventeen years and one at about three years. One other case, entirely well after six years, failed to come, but reported by letter that she was entirely well. The first two were both perineal resections without laparotomy. The last one was a combined one-stage operation with the proximal end brought down to the anal sphincter. He also has a case well and free from recurrence with a permanent inguinal colostomy after five years. His personal cases since 1915, a working period of about eight years, total 44, of these 22 cases were radical resections with 7 deaths.

The method of operation included combined operations in one and two stages, and a few perineal operations without laparotomy. He is inclined to favor the two-stage combined operation as the most ideal, although his best late results chance to be cases in which the perineal operation was done.

Dr. Frank S. Mathews (New York) presented a woman who had been operated on at the age of forty-two for carcinoma of the rectum, eleven and a half years ago, the growth being an annular one felt through the vaginal fornix in the cul-de-sac, but not palpable through the rectum. By an abdominal incision, the growth was removed, the division of the gut beyond the growth being at the floor of the pelvis, so that the distal segment had only a partial peritoneal covering. The proximal segment was inverted about a tube and sutured to it. It was then drawn through the distal segment and, by traction on the tube from below, the upper segment was partly invaginated into the lower. The tube came out in eight days, bowels moved on the ninth, and patient left the hospital in two and a half weeks. The growth infiltrated all the coats of the rectum, but the nodes examined were not involved.

He always precedes a perineal operation by an abdominal exploration to determine the condition of the liver and the regional lymph-nodes, and making a left colostomy which permits one to maintain a cleaner perineal wound and which could be closed later if conditions permitted.

Dr. Allen O. Whipple (New York) presented a woman, who was forty-one years of age when she came to the Presbyterian Hospital on March

16, 1916, complaining of pain in back on evacuation of bowels, loss of weight and strength, diarrhœa of five months' duration. The onset had been gradual with pain in back and pelvis while at stool and feeling of not having completed evacuation of bowels. Began having frequent stools containing blood for two and a half months, four to eight stools a day, considerable blood and mucus. Examination revealed a nodular mass in the rectum ten centimetres above the anus. It was freely movable. The rectum was excised March 27, 1916, by Dr. George E. Brewer.

Dr. George Woolsey (New York) reported the history of a man, who, September 4, 1901, being then forty-three years of age, was admitted to the Presbyterian Hospital on account of bloody discharges from the rectum with pain on defecation. Examination showed just inside the internal anal sphincter an uneven villous-like growth encircling the rectum, more prominent on the right side. It seems continuous with the prostate, which is enlarged. especially the right lobe, which feels nodular and firm. The growth feels hard, the base is infiltrated and irregular, and it is painless on pressure.

September 6, 1901, Doctor Woolsey operated as follows: Left inguinal colostomy.

Five days later, September 11, 1901, a Kraske resection of the rectum was done under gas and ether. The growth was found to extend to about five inches above the anus. Above this point the rectum, after dissecting off the peritoneum, was cut away from the gut above and removed, with the pelvic fat and glands behind it. The upper free end of the gut was then brought down and its mucosa sutured to the free margin of the anal portion, while its outer layers were sutured to the external sphincter to relieve any tension on the mucosal suture. There was practically no tension on the rectum. The wound was lightly packed with gauze, after suturing the upper half of the skin incision. A gauze pad was introduced through the colostomy opening into the distal segment to prevent fæcal matter entering the lower part of the bowel All stools were passed through the colostomy until the sixth day, when the pad was removed. Two weeks after operation the lower end of the gut had separated from the anus by about two inches and fæcal matter passed mostly through the granulating wound, partly through the colostomy. The complete granulation and closure of the posterior wound was a slow process. Four months after operation there was still a small sinus through which part of the fæcal matter was passed. The colostomy was not completely closed.

The *pathological report* was malignant adenoma, invading all tissues. A lymph-node examined showed no invasion by the growth.

About a month ago he was asked by Doctor Whipple to see this man upon whom he had operated twenty-three years ago, who was again under treatment in the hospital on account of a large mass on the left side of the neck, and a smaller one on the right side. Microscopic examination of a specimen from the neck showed Hodgkin's disease. On examining the rectum there was a slight constriction at the level of the internal sphincter, but no sign of recurrence on digital or proctoscopic examination. The colostomy had never been undone and it formed a hernial protrusion, on which, from time to time, a small spot, corresponding to the stoma, would open up and form a very small discharging sinus. He had good control of the bowels, except when they were very loose. He was in the hospital being treated for Hodgkin's disease, when, February 17, he died suddenly from an intestinal hemorrhage, which was shown by autopsy to come from a duodenal ulcer, that had given no symptoms and was not suspected. As a result of the autopsy and the microscopic examination,

Doctor Von Glahn, Pathologist of the Presbyterian Hospital, reports that there is no trace of any recurrence of the new growth, but extensive lesions of Hodgkin's disease.

Dr. John H. Gibbon (Philadelphia) said that notwithstanding the excellent late results following operation for cancer of the rectum in some cases which had been exhibited, this condition remains one of the unsatisfactory fields of surgery. If one is able to remove a rectum fairly early for carcinoma, the ultimate results are remarkably good. The one thing of primary importance in deciding an operability in these cases is the question of metastasis. The size and extent of the growth is not all one wants to know, especially in young people. He had been so astonished to find early metastasis to the liver in people of thirty to forty years of age without any evidence of it that he determined long ago never to do an operation on the rectum without opening the abdomen. This eliminates the posterior operations unless preceded by this earlier exploration. An anterior colostomy is more comfortable than a posterior and, as far as function is concerned, is much better. Many of the far-advanced cases live as long without operation as with it. No case with metastasis should be subjected to a radical operation. His experience in trying to preserve the sphincter had been very unsatisfactory; these resulted in either stricture or incontinence.

Dr. Damon B. Pfeiffer (Philadelphia) said that one of the chief reasons why this subject is in the chaotic state it is, is because of the extraordinary variation in pathology and clinical behavior of different growths in different individuals. Carcinoma varies quite as much as any disease. He recalled a woman operated on sixteen years ago for a small carcinoma of the rectum above the internal sphincter, who is alive to-day and free from recurrence. Four years ago he had in the same hospital and at the same time two patients, a man and a woman, who each had a growth, which had been apparent for one year, completely encircling the bowel. The growths were small and freely movable and the outcome seemed favorable. The same operation was done on both. The man developed large metastases and died in six months. The woman showed no metastasis and is alive to-day. That factor of variability of pathology should always be borne in mind in considering which operation will fit the case. Many recoveries are on record from different sorts of operations and the factor of malignancy has been disregarded. There is a definite etiological picture connected with malignancy. It exists primarily whether it can be recognized microscopically or not, and it has to be taken into consideration when deciding which operation will give the best results. In spite of the recorded successes of the different operations, it has become clear that if one is to have notable successes that can be expressed in terms of percentages rather than in terms of results, one must achieve it the same as with carcinoma in other fields; one must consider the zones of spread, the natural path of metastasis. He was very pleased to hear that anyone could report ten successful cases of combined abdominal and perineal excision. Fifteen years ago this number of cases without mortality would have been astonish-

ing. Miles, the chief exponent of this combined operation, has confessed to 20 per cent. mortality and in general hands the mortality would be higher than that. The work on cancer of Francis Miles, of England, the Mayos, and of Doctor Jones, of Boston, is spreading the gospel of complete operation. A two-stage operation can sometimes be done where one cannot be attempted in the average hands. One must remember that many of these patients are in a state of impaired vitality. One should remember that many such patients cannot stand successfully a complete operation in one stage. Finally, one must remember that the technic of the combined operation must be thoroughly learned before it is applied, to avoid loss of time, loss of blood, shock and infection and control of the spread of infection. The speaker's own failures had been due to his not applying these underlying principles. On the other hand, he had been fortunate enough not to lose cases where he had not transgressed any of these principles. He believed the aim of those devoting their time to surgery of the rectum should be to secure mortality rates which would compare favorably with surgery in other conditions, such as gastric carcinoma.

Dr. Daniel F. Jones (of Boston) said that he had been an advocate of the combined abdomino-perineal operation for carcinoma of the rectum for many years. The combined abdomino-perineal operation in one stage is, he believes, the ideal operation, but it is true that the operation is not suitable for every patient, and if one wishes to operate upon the highest possible percentage of the patients seen, one must choose a suitable operation for each patient.

As many patients are too old or too feeble to stand the one-stage combined abdomino-perineal, he has developed a two-stage combined abdomino-perineal operation which may be used in a certain number of those who cannot stand the operation in one stage. There are some too old or too feeble to stand the operation in two stages; then a colostomy is done and some weeks later amputation by the perineal route as recently advocated by Lockart-Mummery.

There are a few cases in which the growth is sufficiently high to use the operation suggested by W. J. Mayo, in which the dissection is carried down below the growth by the abdominal route, the bowel sectioned below the growth, and the proximal end brought out, after removal of the growth, for a permanent colostomy, and the distal end closed.

Radium must be considered in the treatment of carcinoma of the rectum, but it should be confined to those too old, too feeble, or too fat for operation, and to the inoperable cases. In these the sphincter is removed, except in a very few carefully selected cases. If it is left it may be so weakened as to be valueless and a stricture may result, or a sinus may remain. The patient is more uncomfortable with a sphincter that does not control, or a fistula, than he would be with a good colostomy, but the chief reasons for doing a permanent colostomy is that in leaving the sphincter one is always tempted to section the bowel too close to the growth, either above or below. Another reason is

that the recurrence is frequently in the pelvis and this may involve the bowel and cause obstruction a second time.

Some one has said that these patients frequently live for years without operation and implied that it might not be necessary to operate. Because they do live so long and are so uncomfortable while they do live is one of the chief reasons for operating.

Removal of the growth should be undertaken even though it is evidently nothing more than a palliative operation. Colostomy alone does not give the comfort that excision of the growth does. The combined abdomino-perineal operation has been done in the presence of small nodules in the liver. These patients usually live a year or more and six months of comfort repays one for going through the operation.

The speaker has for several years been looking for statistics on various operations for cancer of the rectum and felt fortunate in getting the statistics for the perineal operation at St. Mark's Hospital, London, as presented by Gabriel in the January, 1925, issue of the British Journal of Surgery, to compare with the statistics in the combined abdomino-perineal operation. The figures without brackets in the tables are the figures from St. Mark's Hospital, London, as given by Gabriel for the perineal operation, while those in brackets are for the combined abdomino-perineal operation by the speaker.

TABLE I

Cases Grouped According to the Length of Time which has Elapsed Since Operation

	Less than 3 years after operation	Between 3 & 5 years after operation	More than 5 years after operation	Totals
Number of cases	58 (19)	22 (16)	63 (22)	143 (57)
Immediate mortality	7 (1)	6 (0)	9 (3)	22 (4)
Subsequent mortality	8 (3)	9 (6)	27 (7)	44 (16)
Untraced	1 (0)	1 (0)	11 (1)	13 (1)
Alive with recurrence	3 (1)	1 (1)	1 (0)	5 (2)
Alive and well	39 (14)	5 (9)	15 (11)	59 (34)

TABLE II

A Comparison of Immediate Mortalities. Perineal and Abdomino-perineal Operations

	Number of cases	Operability rate	Mortality
Perineal	143	44%	15.4%
Abdomino-perineal	(57)	(60%)	(7%)

TABLE III

Comparison of Perineal and Abdomino-perineal Operations as to Percentage of Cures

Descriptions	3 year cases	5 year cases
(*a*) Figures based on total numbers submitted to operation	23.5% (44%)	24% (41%)
(*b*) Figures based on survivals from operation	28.5% (50%)	28% (52%)

Dr. William C. Lusk (of New York) said he would like to say a friendly word in favor of saving the sphincters in suitable cases, and doing the ideal operation of resection of the rectum in which the sigmoid flexure is liberated by the abdominal route, and brought down and united by circular interrupted sutures to the distal rectal segment above the internal sphincter by the posterior route. The cases for which this operation might be suitable seemed to him to be those of early carcinomata which were situated sufficiently high above the internal sphincter. He operated on such a case in June, 1910, and the wound healed without any stricture of the rectum and with perfect function of the sphincters. This man was alive and well to-day. (See "Resection of the male rectum for cancer by the combined method in two stages; first stage under Spinal Anæsthesia," Annals of Surgery, December, 1910.) He had illustrated this operation. ("A Technic of Resection of the Male Rectum"; *Surgery, Gynecology and Obstetrics,* November, 1909.)

Doctor Lusk said that Doctor Whipple's experience with cæcostomy and appendicostomy, as preliminary operations before rectal excision, had corresponded with his own experience with what he called the left subcostal colonic vent, which was a tube-sinus established in the descending colon just below the tip of the left eleventh rib, in advance of the operation for removal of the rectum. This site for the fistula was well apart from the lower abdominal wounds. He showed pictures illustrating the construction of the vent. (Technic: Through an incision half an inch below and parallel to the left eleventh rib, the peritoneum is opened opposite the tip of the eleventh rib, and the opening enlarged backward to the site of reflection of the peritoneum onto the descending colon. The lower edge of the peritoneum is then drawn outward over the entire thickness of the cut muscles of the lower lip of the wound in the abdominal wall and fixed in this position with sutures. A cone-shaped fold of the descending colon, caught up by a thread, is then pulled outward over the everted lower peritoneal flap, to which latter its base and margins are sutured so as to maintain its protrusion. The upper edge of the peritoneal opening is first sewed to the deep margin of the transversalis muscle, and then below to the base of the cone-shaped protrusion of the bowel along the line of its emergence from the peritoneal cavity, and beyond the bowel protrusion, to the lower flap of the peritoneum. Two loops of Pagenstecher thread are inserted into the exposed surface of gut to locate the site for subsequent puncture. The angles of the wound may be drawn together. Gauze is inserted to prevent adhesions from taking place over the exposed bowel surface.)

The advantages of this fistulous opening are the following: Before the operation for removal of the rectum, (1) the portion of the bowel above the tumor could be washed out, and also (2) gas from the intestines would escape, leaving the belly flat. In one case of rectal extirpation which he had operated upon with this preliminary device, the intestines were so flat, that when he sutured together the abdominal wound, an air space was left

within the peritoneal cavity. At the operation, in the presence of this vent, (3) an artificial anus could be sewed up tight without opening for several days, while the wounds were healing; (4) when the artificial anus was then opened, the size of the aperture could be regulated. Following the operation, a most important feature was that (5) as soon as the patient was put to bed, water could be introduced into the bowel, and (6) post-operative intestinal distention was prevented. During convalescence (7) the lower bowel was handily cleansed by enemas given through this vent. Thus the vent gave much comfort to the patient, lessened the dangers of the operation, and as well lessened the anxiety of the operating surgeon.

He said one problem he wished to mention was the existence with comparative frequency of a narrow pelvic cavity, which latter could be so narrow that it was impossible to get the knuckles within it through the posterior route, where the sacrum was cut across through the fifth sacral vertebra. Johae (*Beiträge f. klin. Chir.*, vol. x, 1893, p. 755) had determined a relationship between the distance between the posterior superior spines of the ilium and the size of the pelvic cavity. Doctor Lusk said that he had confirmed the truth of this relationship by anatomical study on cadavers, he having found that if the distance between the inner surfaces of the posterior superior iliac spines was as great as 2¾ inches, then in the cadavers in the absence of any tumor of the rectum, the superior hemorrhoidal vessels could be reached and tied through the posterior route; but when this distance was as small as 2½ inches, that then one attempting to tie the superior hemorrhoidal vessels through the posterior route was sure to have trouble from lack of room. He regarded that the narrow pelvic cavity was a big problem in rectal extirpation. To in part meet the difficulties in the presence of this condition, he thought that at least the superior hemorrhoidal vessels should be tied, and the lateral pelvi-rectal fascial attachments isolated and cut downward as far as possible, and the peritoneum all around the rectal segment severed, if possible, by the abdominal route, to facilitate removal from below. In an extreme case, the possibility of a resort to symphysiotomy had occurred to him. He had once bisected the sacrum up to the level of the third sacral foramina, fracturing the sacrum across at the latter level and reflecting the two halves outward, without gaining workable space.

LATE RESULTS OF RESECTION OF THE ŒSOPHAGUS FOR CARCINOMA

Dr. Franz Torek (New York) said that in discussing the late results of resection of the œsophagus for carcinoma he would confine his remarks to the resection of the thoracic portion of the œsophagus. When one considers the late results of this procedure one is interested in the length of time the patient has lived after operation, the degree of comfort or discomfort since operation, the influence on the patient's general health, the question of complications caused by the operation, and the question of recurrence of the disease. He presented a patient, who was operated on March 14, 1913, so that in two and a

half weeks from to-day, twelve years will have elapsed; therefore, on the first point mentioned, the length of life after operation, her presence to-day renders favorable testimony.

To consider intelligently the other points in this presentation, it will be necessary to outline in a few words what the operation consists in. The thoracic cavity is opened on the left side by an incision through almost the entire length of the seventh intercostal space and the division of four ribs from the seventh up to near the spinal column. This gives ample room for access. The œsophagus is liberated from the diaphragm to the neck and divided between two ligatures beneath the tumor. The lower end is invaginated by one or two purse-string sutures, the upper part, inclusive of the tumor, is exenterated through an incision at the anterior border of the left sterno-cleido-mastoid muscle. Then that portion of the œsophagus above the tumor which is to be retained, is placed antethoracically under the skin, the cut end being sutured to an incision in the skin of the thorax. Anything that is swallowed therefore passes down the œsophagus and out through the incision in the skin, to which the cut end was sutured. To lead the food into the stomach a rubber tube is employed, which bridges the gap from the œsophageal fistula to a gastrostomy opening. The case was described in *Surgery, Gynecology and Obstetrics;*[1] a more extensive article appeared in ANNALS OF SURGERY,[2] and a follow-up report in *Archives of Surgery.*[3]

Now, as to the question of comfort, the presence of the foreign material, the rubber tube, causes her neither pain nor discomfort. She eats all kinds of food; it glides down readily after thorough chewing. She is not subjected to the passage of bougies, one of the unpleasant accompaniments of attempts at plastic restoration of the œsophagus; nor is she exposed to the necessity for reoperations, which almost always arises in œsophagoplasties owing to strictures that result in spite of frequent passage of bougies. All she has to do is to replace the rubber tube by a new one once a month and to cleanse it every four or five days.

The third point, the effect on the general health, if judged by this patient, leaves nothing to be desired. She has all these years been about as well as a person of her age can be expected to be. Her digestion is satisfactory, and, as compared with that of a person fed through a gastrostomy tube and funnel, it is only natural that her digestion should be better, as she gets the benefit of the admixture of her saliva with the food. In fact, as she has to chew more thoroughly than an ordinary person, the salivary digestion is apt to be even better than the average.

[1] Torek, Franz: The First Successful Case of Resection of the Thoracic Portion of the Œsophagus for Carcinoma. Surgery, Gynecology and Obstetrics, June, 1913.

[2] Torek, Franz: The Operative Treatment of Carcinoma of the Œsophagus, ANNALS OF SURGERY, April, 1915.

[3] Torek, Franz: Carcinoma of the Thoracic Portion of the Œsophagus. Report of a Case in which Operation was Done Eleven Years Ago. Archives of Surgery, vol. x, No. 1, Part 2.

As regards possible complications due to the operation, we might expect some pulmonary or pleural affection owing to the extensive opening of the chest and the manipulation within it.

Lastly, as to the question of recurrence. This depends on two conditions, first, the degree of malignancy of the new growth; secondly, the thoroughness of its surgical removal. In carcinoma of the œsophagus the degree of malignancy of the lesion on the mucosa, pathologically studied, is low, the most frequent form being acanthoma, the type being embryonal, with prickle cells often missing. The adeno-carcinomatous type is less frequent. Clinically, the malignancy becomes greater as the lesion extends; in the later stages metastases occur, and when the carcinoma has extended through all the coats of the œsophagus, involvement of the mediastinum, the pleuræ, and the lungs will drag the patient down rapidly. Therefore, to avail one's self of the comparative benignity of the lesion, it is necessary to attack it early. The other condition for securing freedom from recurrence, the thoroughness of surgical removal, requires that the operation be so planned as to secure good access and proper exposure. The transpleural route described secures that access and exposure to a greater degree of certainty than any other, as it exposes the entire thoracic œsophagus. The full extent of the lesion cannot always be definitely determined by our diagnostic methods, including röntgenographic study, therefore a previously planned limited exposure of the new growth may turn out to be insufficient. In Lilienthal's case of extrapleural resection the interpretation of the X-ray picture led to an insufficient exposure of the carcinoma and consequent scant resection at one end of the tumor. But for this slight error in estimating the necessary extent of exposure Doctor Lilienthal's patient would not have had a recurrence and would be alive now.

The late results, as far as recurrence is concerned, therefore, will be good if the new growth is attacked before it becomes clinically malignant, and if the operation is so planned as to permit resection with a good margin.